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Julia-Kocienski Approach to Trifluoromethyl-Substituted Alkenes¹

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Abstract

A Julia-Kocienski approach to trifluoromethyl-substituted alkenes was evaluated in the reactions of 1,3-benzothiazol-2-yl, 1-phenyl-1*H*-tetrazol-5-yl, and 1-*t*-butyl-1*H*-tetrazol-5-yl 2,2,2-trifluoroethyl sulfones with aldehydes. Among the various conditions tested, the best yields were obtained with 1-phenyl-1*H*-tetrazol-5-yl 2,2,2-trifluoroethyl sulfone, in CsF-mediated, room temperature olefinations in DMSO. Aromatic aldehydes gave (trifluoromethyl)vinyl derivatives in 23-86% yields, with generally moderate stereoselectivity. Straightforward synthesis of the Julia-Kocienski reagent, and conversion to trifluoromethyl-substituted alkenes under mild reaction conditions, are the advantages of this approach.

Selective fluorination of organic molecules is highly important for pharmaceuticals and agrochemicals, due to the remarkable influence fluorine can have on bioactivity.³ In these contexts, trifluoromethyl-substituted alkenes are of synthetic value as intermediates, or as biologically active end products (e.g. bifenthrin, an insecticidal pyrethroid). However, synthetic approaches to (trifluoromethyl)vinyl derivatives are relatively under-explored. Among the various methods, metal-mediated approaches to vinyl trifluoromethylation include: (a) Pd-catalyzed reactions of vinyl sulfonates with TMS- or TES-CF₃,⁴ (b) Cu-catalyzed reactions of vinyl bromides with TMS-CF₃,⁵ (c) Fe- and Cu-catalyzed reactions of vinyltrifluoroborates and vinylboronic acids with Togni's reagent,^{6,7} (d) Cu-catalyzed reaction of vinyl boronic acid with Umemoto's reagent,⁸ (e) Cu-catalyzed decarboxylative trifluoromethylation with Togni's reagent,⁹ (f) Cu- and Fe-catalyzed decarboxylative trifluoromethylation with Langlois reagent,^{10,11} (g) Heck-like reaction on *in situ* formed 3,3,3-trifluoropropene,¹² (h) Hiyama reaction of aryl iodides with (*E*)-trimethyl-(3,3,3-trifluoroprop-1-enyl)silane,¹³ (i) redox-chemical methods involving Ir¹⁴ and Ru^{15,16} catalysts. Wittig- and Horner-type reactions have also been evaluated as approaches to vinyl trifluoromethylated compounds. For example, the TBAF-mediated condensation of aldehydes with Ph₂P(O)CH₂CF₃¹⁷ as well as synthesis of Ph₃P⁺CH₂CF₃•OTf[−] and its reaction with aldehydes promoted by CsF,¹⁸ have been reported in the literature.

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Interestingly, the Julia-Kocienski approach¹⁹ to trifluoromethyl-substituted alkenes has not been reported to date, although its potential for the preparation of various types of fluoroalkenes has been demonstrated.²⁰ Herein, we report our results on the synthesis of (trifluoromethyl)vinyl compounds via such an approach.

In order to evaluate the use of Julia-Kocienski olefination reactions, synthesis of a series of heteroaryl sulfones, i.e. 1-phenyl-1*H*-tetrazol-5-yl 2,2,2-trifluoroethyl sulfone (PT-sulfone), 1,3-benzothiazol-2-yl 2,2,2-trifluoroethyl sulfone (BT-sulfone), and 1-*tert*-butyl-1*H*-tetrazol-5-yl 2,2,2-trifluoroethyl sulfone TBT sulfone, was undertaken (Table 1).

Next, condensation conditions were screened in reactions of heteroaryl sulfones **2a–c**, with 2-naphthaldehyde (Table 2). Reaction of PT-sulfone **2a** in the presence of DBU gave a low 7% yield of **3** (entry 1). Under basic conditions, elimination of fluoride from heteroaryl sulfones **2a–c** is possible (*vide infra* Scheme 1 and discussion) leading to difluoro olefin **4**, which represents a dead end intermediate. Therefore, addition of a source of F[–] was considered in order to reverse this elimination. This has previously been demonstrated in Wittig- and Horner-type syntheses of (trifluoromethyl)vinyl compounds, mediated by TBAF or by CsF.^{17,18} Indeed, TBAF-mediated condensation of **2a** in acetonitrile at room temperature increased the yield to 34%, but a lower selectivity was observed (entry 2). Changing the solvent to THF increased the yield and selectivity (entry 3). BT-sulfone **2b** gave a comparatively lower yield in the TBAF-mediated reaction in THF at room temperature, and a marginally better selectivity (entry 4). Lowering of the reaction temperature to 0 °C marginally increased the yield and selectivity (compare entries 4 and 5). Reaction of **2b** mediated by TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate) in CH₂Cl₂ gave both a lower yield and selectivity (entry 6). Next, CsF was tested (entries 7–9) in the reactions of sulfones **2a–c**. Condensations were performed in DMSO at room temperature, and among the three sulfones **2a** gave the highest yield (entry 7). Olefination with BT-sulfone **2b** gave a lower yield and selectivity (entry 8), whereas reaction with TBT-sulfone **2c** proceeded with best selectivity, but in a much lower yield (entry 9). The yield and selectivity in the TBAF-mediated reaction of **2a** in DMSO were similar to those obtained in CsF-mediated reaction (compare entries 7 and 10).

There was one other problem in these fluoride-mediated condensations. In the presence of moisture, 2-vinylnaphthalene (**7**) was formed, plausibly via the Julia intermediate **6**. As shown in Scheme 1, initial conjugate addition of water to vinyl sulfone **4**, produced by loss of fluoride, can result in difluorohydrin **5**. Multiple pathways are available for the formation of intermediate **6** from compound **5**. In one pathway, expulsion of HF can result in an acyl fluoride that can undergo hydrolysis, followed by decarboxylation. Alternatively, difluorohydrin **5** could fragment by loss of carbonyl fluoride (COF₂), and reaction of the latter with H₂O leads to CO₂ and HF. Formation of both acyl fluoride and carbonyl fluoride upon reaction of nucleophiles with difluorovinyl compounds has been reported.^{21,22} Condensation of **6**, generated by such pathways, with 2-naphthaldehyde would then produce 2-vinylnaphthalene (**7**). This problem was more pronounced under TBAF-mediated reactions, than when CsF was employed as the base. This is not surprising due to the lower hygroscopic nature of CsF as compared to TBAF. We therefore decided to pursue olefinations using CsF in DMSO.

With the optimization reactions completed, a series of aldehydes were reacted with PT-sulfone **2a**, under CsF-mediated conditions in DMSO at room temperature. The scope of these olefinations is shown in Table 3. Condensation reactions seem to be highly substrate dependent. Use of 1-naphthaldehyde instead of 2-naphthaldehyde gave a lower yield, with no *E/Z* selectivity (compare entries 1 and 2). Extending the aromatic core to the phenanthrene system resulted in a slight lowering of yield (entry 3) but the product yield with the isomeric 9-anthraldehyde was better (entry 4). The *E/Z* ratio in the case of the latter was significantly in favor of the *E*-isomer. This could possibly be due to unique substrate structure, that could favor formation of highly stabilized zwitterionic intermediates leading to the trans alkene via an E1 elimination path.²⁰ The reaction of pyren-1-carboxaldehyde proceeded in a better yield and the *E/Z* ratio paralleled the phenanthrene carboxaldehyde reaction (entry 5). Electron-withdrawing groups on the aromatic ring produced acceptable product yields (entries 6–8) but low yield was obtained with 3-methoxybenzaldehyde (entry 9). The highly electron-rich 4-methoxybenzaldehyde did not afford any product. Interestingly, 6-methoxy-2-naphthaldehyde produced an acceptable product yield (entry 10). Most surprisingly, 4-phenylbenzaldehyde gave the lowest yield in the series (entry 11). Ring electronics appear to play little role, if any, in the stereoselection because the electron-rich and electron-deficient aldehydes gave comparable *E/Z* product ratios. Reactions with an alkyl aldehyde (*n*-octanal) and a cinnamaldehyde were unsuccessful.

An initial attempt at isomerization of the *E/Z*-**3** alkene mixture under I₂-catalyzed conditions did not produce a change in the ratio.²⁴

In summary, we have demonstrated that the Julia-Kocienski olefination offers a relatively straightforward route to (trifluoromethyl)vinyl compounds despite the problem of fluoride expulsion as well as the formation of protio vinyl products. Yields are substrate-dependent, whereas stereoselectivities generally are not. Facile synthesis of reagent and mild olefination conditions are clear advantages of such an approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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23. Condensation of 2a with 6-methoxynaphthalene-2-carboxaldehyde: To 6-methoxynaphthalene-2-carboxaldehyde (93.1 mg, 0.500 mmol, 1.0 molar equiv), PT-sulfone 2a (73.0 mg, 0.25 mmol, 0.5 molar equiv), and anhydrous CsF (190 mg, 1.25 mmol, 2.5 molar equiv), was added anhydrous DMSO (10.0 mL), and the reaction mixture was stirred at room temperature. After 1 h, 2a (73.0 mg, 0.25 mmol, 0.5 molar equiv) and CsF (190 mg, 1.25 mmol, 2.5 molar equiv) were added, and this step was repeated two more times, until a total of 292 mg (1.00 mmol, 2.0 molar equiv) of 2a and 760 mg (5.00 mmol, 10.0 molar equiv) of CsF were used in the reaction. After 19 h, water (5.0 mL) was added to the reaction mixture, and the mixture was extracted with EtOAc (3 × 20.0 mL). The combined organic layer was washed with water (3 × 15.0 mL), followed by brine, dried over anhydrous Na₂SO₄, and the solvent was evaporated under reduced pressure. Purification by column chromatography (SiO₂, 12% EtOAc in hexanes) yielded E/Z-16 (64.3 mg, 51%) as an off-white solid.
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Scheme 1.

Two problems to contend with in the olefination reaction

Table 1

Synthesis of 2,2,2-trifluoroethyl heteroaryl sulfones

Entry	Yield of 1 ^a	Oxidation Conditions	Yield of 2 ^b
1	1a : 90%	cat CrO ₃ , H ₅ IO ₆ , CH ₃ CN, rt	2a : 83%
2	1b : 87%	m-CPBA, CHCl ₃ , rt	2b : 90%
3	1c : quant	cat. Mo ₄ O ₂₄ (NH ₄) ₆ •4H ₂ O, H ₂ O ₂ , EtOH, rt	2c : 69%

^aYield of the crude product. The crude sulfide was used in the oxidation.

^bYield is of isolated and purified products.

Table 2

Screening of Olefination Conditions of Heteroaryl Sulfones with 2-Naphthaldehyde

Entry	Sulfone	Conditions	Yield of 3 (%) ^a	% <i>E/Z</i> ^b
1	2a	DBU, CH ₂ Cl ₂ , rt	7	28:72
2	2a	TBAF, ^c CH ₃ CN, rt	34	37:63
3	2a	TBAF, ^c THF, rt	47	31:69
4	2b	TBAF, THF, rt	27	27:73
5	2b	TBAF, THF, 0 °C	29	20:80
6	2b	TASF, CH ₂ Cl ₂ , rt	23	35:65
7	2a	CsF, DMSO, rt	86	41:59
8	2b	CsF, DMSO, rt	58	44:56
9	2c	CsF, DMSO, rt	40	30:70
10	2a	TBAF, DMSO, rt	85	40:60

^aYield is of isolated and purified products.^bDetermined by ¹⁹F NMR.^cDried for 4 h under vacuum.

Table 3

Reactions of PT-sulfone 2a with various aldehydes.^a

Entry	Aldehyde	Product	Yield ^b (%)	%E/Z ^c	¹⁹ F NMR ^d <5 δppm
1			3: 86	41:59	E: -63.7 Z: -57.8
2			8: 65	52:48	E: -63.9 Z: -58.3
3			9: 42	56:44	E: -63.9 Z: -58.2
4			10: 50	92:8	E: -64.4 Z: -61.7
5			11 : 62	61:39	E: -63.6 Z: -58.3
6			12 : 50	38:62	E: -64.2 Z: -58.2

Entry	Aldehyde	Product	Yield ^b (%)	%E/Z ^c	¹⁹ F NMR ^d <5 δppm
7			13 : 42	39:61	<i>E</i> : -64.4 <i>Z</i> : -58.2
8 ^e			14 : 52	37:63	<i>E</i> : -64.4 <i>Z</i> : -58.2
9			15 : 37	39:61	<i>E</i> : -63.9 <i>Z</i> : -57.9
10			16 : 51	44:56	<i>E</i> : -63.4 <i>Z</i> : -57.8
11			17 : 23	40:60	<i>E</i> : -63.7 <i>Z</i> : -58.0

^a For a representative procedure, please see ref 23.

^b Yields are of isolated and purified products.

^c Determined by ¹⁹F NMR of the crude reaction mixtures.

^d Referenced to CFC1₃ as an internal standard.

^e Sulfone **2a** was used as the limiting reactant, see the Supporting Information for details.