## LETTERS 2012 Vol. 14, No. 9 2286–2289

**ORGANIC** 

## Simple Synthesis of $\beta$ -Trifluoromethylstyrenes Using (*E*)-Trimethyl-(3,3,3-trifluoroprop-1-enyl)silane

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Received March 21, 2012

ABSTRACT



(*E*)-Trimethyl-(3,3,3-trifluoroprop-1-enyl)silane (1) was synthesized as a reagent for use in Hiyama cross-coupling reactions for the production of  $\beta$ -trifluoromethylstyrene derivatives. Cross-coupling of 1 with electronically diverse aryl iodides was achieved by treatment with CsF in the presence of catalytic amounts of palladium to afford the desired products in moderate to good yields.

Trifluoromethylation of materials such as pharmaceuticals, agricultural chemicals, and functional materials significantly improves their performances in most cases.<sup>1</sup> This is exemplified by the fact that more than 150 fluorinated drugs have come on the market in the past 50 years and now account for about 20% of all pharmaceuticals.<sup>2</sup> The trifluoromethylation of carbonyl groups and aryl halides has been intensively investigated. Excellent progress has been made in the catalytic trifluoromethylation of aryl halides and is now a well-established research area.<sup>3</sup> Although much success has been achieved with regard to trifluoromethylation, there are still few reactions for constructing 3,3,3-trifluoropropynyl or propenyl substructures, despite the robust methodology involving threecarbon-elongation reactions. There have been some reports of 3,3,3-trifluoropropynylation using 2-bromo-3,3, 3-trifluoropropene<sup>4,5</sup> and 1,1,1,3,3-pentafluoropropane<sup>6</sup> as three-carbon building blocks. They can be converted in situ into (3,3,3-trifluoropropynyl)lithium which can add to carbonyl compounds or couple with aryl halides through a zinc intermediate. Despite the commercial availability of these materials for three-carbon building blocks, the widespread application of such processes, especially in industry, has been hindered by the low boiling points of the materials,

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making them difficult to handle, in addition to their cost and the need to use excess alkyllithium in preparing 3,3,3trifluoropropynyllithium. On the other hand, there have been very few reports on 3,3,3-trifluoropropenylation of aryl halides leading to  $\beta$ -trifluoromethylstyrenes, which have been used for organic light-emitting diodes and other materials chemistry applications. In 1981, Fuchikami et al. reported the synthesis of  $\beta$ -trifluoromethylstyrenes using palladium-catalyzed cross-coupling reactions of 3.3.3-trifluoropropene with aromatic halides.<sup>7</sup> However, the use of gaseous 3.3.3-trifluoropropene requires the use of an autoclave for the reaction, and the substrate scope is limited. Very recently, Prakash et al. reported the synthesis of  $\beta$ -trifluoromethylstyrenes through a Heck coupling reaction of aryl iodides with 1-iodo-3,3,3-trifluoropropane.<sup>8</sup> The reaction has advantages that include 1-iodo-3.3.3-trifluoropropane is a liquid at room temperature and the substrate scope is not limited. Unfortunately, the reaction requires a microwave reactor capable of maintaining a temperature of 200 °C under microwave irradiation. We therefore focused on the development of a simple protocol for the introduction of a 3,3,3-trifluoropropenyl unit into an aryl halide.

**Figure 1.** Structure of key molecule (1) for 3,3,3-trifluoropropenylation in Hiyama cross-coupling reaction.

We chose trimethyl-(3,3,3-trifluoroprop-1-enyl)silane (1) as the building block for 3,3,3-trifluoropropenylation of aryl halides (Figure 1). It has the advantage of being easy to handle, and it is applicable to Hiyama cross-coupling reactions. To our knowledge, there have been no reports of practical large-scale preparations of 1, although there have been a few reports of inefficient syntheses or its formation as a side product.<sup>9</sup> The aim of our study was to establish a synthetic strategy for the production of **1**. In the strategy, which is shown in Scheme 1, a trifluoromethyl unit was supplied with trifluoroacetaldehyde generated from trifluoroacetaldehyde ethyl hemiacetal and sulfuric acid. The key intermediate 3, which contains the backbone of 1, was constructed in the first reaction. The subsequent reactions, mesylation of 3 followed by elimination, afforded 1, but isolation of 1 from the reaction mixture was difficult because of the somewhat high volatility of 1. This problem was circumvented by conducting the reaction without any solvent, and consecutive distillations of the crude mixture gave 1 as a pure liquid. This protocol has advantages that include a high chemical yield of 1(74%) achieved over three steps and applicability to gram-scale syntheses. In terms of physical propensities, **1** is volatile to some extent but is a manageable liquid at atmospheric pressure and suitable for long-term storage in a sealed flask under refrigeration.

## Scheme 1. Synthesis of 1



 Table 1. Investigation of Reaction Conditions Suitable for

 Hiyama Cross-Coupling Reaction of 1 with *p*-Iodoanisole

cat Pd<sup>0</sup>

-CF<sub>3</sub>

I	H <sub>3</sub> CO 5a (1 equiv)	quiv) F anion solvent 80 °C	H₃CO	」 6a	
entry	catalyst (mol %)	F anion (equiv)	solvent	time (h)	6a yield $(\%)^{a,b}$
1	Cu (120) <sup>c</sup>	CsF (2)	DMF	4	_
2	$Pd(PPh_3)_4(5)$	CsF(2)	DMF	2	31
$3^d$	$Pd(PPh_3)_4(5)$	CsF(2)	DMF	2	_
$4^e$	$Pd(PPh_3)_4(5)$	CsF(2)	THF	4	_
$5^{f}$	$Pd(PPh_3)_4(5)$	CsF(4)	DMF	3	40
6	$Pd(dppe)_2(5)$	CsF(2)	DMF	3.5	92
7	$Pd(dppe)_2(5)$	CsF(2)	DMA	3.5	26
8	$Pd(dppe)_2(3)$	CsF(2)	DMF	5	92
					(85)
9	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	CsF(2)	DMF	3.5	98
	$P(mesityl)_3(15)$				(86)
10	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	CsF(2)	DMF	2	50
	Xantphos (9)				
11	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	KF(2)	DMF	2	23
	P(mesityl) <sub>3</sub> (15)				
12	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	KF (2)/	DMF	14	21
	$P(mesityl)_3(15)$	BnBu <sub>3</sub> NCI (1)			
13	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	TBAF(2)	DMF	24	21
	$P(mesityl)_3(15)$				
14	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	TASF $(2)$	DMF	2	41
	$P(mesityl)_3(15)$				
$15^g$	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	TASF $(2)$	THF	2	_
	$P(mesityl)_3(15)$				
$16^e$	Pd <sub>2</sub> (dba) <sub>3</sub> (1.5)/	TASF $(2)$	THF	2	7
	$P(mesityl)_3$ (15)				

<sup>*a*</sup> NMR yields, which were calculated by <sup>19</sup>F NMR integration of products **6** relative to the internal standard of ethyl 2,2,2-trifluoroacetate. <sup>*b*</sup> The values in parentheses indicate the isolated yields of **6**. <sup>*c*</sup> 1,10-Phenan-throline was added for a ligand of Cu. <sup>*d*</sup> The reaction was conducted at 40 °C. <sup>*e*</sup> The reaction was conducted in refluxing THF. <sup>*f*</sup> 4 equiv of **1** were used. <sup>*g*</sup> The reaction was conducted at rt.

The chemical reactivity of **1** was investigated using a transition-metal-catalyzed Hiyama cross-coupling with

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<sup>*a*</sup>NMR yields, which were calculated by <sup>19</sup>F NMR integration of products **6** relative to the internal standard of ethyl 2,2,2-trifluoroace-tate. <sup>*b*</sup> The values in parentheses indicate the isolated yields of **6**.

4-iodoanisole.<sup>10</sup> The reaction did not take place using a stoichiometric amount of Cu powder ligated with 1,10-Phen in the presence of CsF to dissociate the  $Si-C_{sp^2}$  bond (entry 1, Table 1). A catalytic amount of palladium(0) resulted in a reaction affording coupling product **6** in low

yield (entry 2). Notably, lowering the temperature from 80 to 40 °C hindered the reaction, and desilylation seemed to be difficult or seriously retarded (entry 3). The solvent also significantly influenced the reactivity, and the reaction did not proceed in THF (entry 4). Increasing the amount of CsF to 4 equiv with respect to 1 did not result in a large increase in yield, increasing it from 31% to 40% (entries 2 and 5). The use of palladium with a bidentate ligand, dppe, improved the yield dramatically, to 92%. We assumed that the *cis*-oriented ligand would accelerate the reductive elimination of the palladium(II) intermediate to generate a new C–C bond on **6**, enabling the palladium(0) dosage to be reduced from 5% to 3% (entries 6 and 8).

The optimal yield was obtained using a palladium catalyst with a bulky ligand, trimesitylphosphine, affording 6 in 98% yield (entry 9). We expected xantphos to be an excellent ligand because it is bidentate and bulky, but use of this ligand reduced the yield of 6 to 50% (entry 10). These results suggest that the performance of the palladium catalyst governed the reaction to a considerable extent and that the bulky trimesitylphosphine ligand is the optimal ligand for this reaction. A reaction temperature of around 80 °C is also crucial for desilylation, to generate a vinyl anion species. Other fluoride sources, KF, TBAF, and TASF, were also assessed for the reaction. Under the optimal conditions, the use of KF in the reaction considerably decreased the yield of 6, to 23% (entry 11). In situ generated tetraalkylammonium fluoride from KF and corresponding ammonium chloride was not suitable for the reaction (entry 12).<sup>11</sup> TBAF and TASF were not good fluoride sources either, although the production of nucleophilic naked fluoride ions was enabled due to distinctive features (entries 13–16).

In terms of the Hiyama cross-coupling reactions, alkenyltrialkylsilanes are unreactive in the alkenylation of aryl halides under the usual reaction conditions because they are not inherently electrophilic to become the silicate(V or VI) unless the more nucleophilic TASF must be used. Alkenylsilanes susceptible to nucleophilic attack, such as alkenylsiloxanes,<sup>12</sup> alkenylsilacyclobutanes,<sup>13</sup> or alkenylsilanols,<sup>14</sup> are therefore used as the alkenylation reagent. In contrast, **1** participates in Hiyama cross-coupling reactions under mild conditions, although **1** contains trimethylsilane. We assumed that the inductive effect of the electronwithdrawing trifluoromethyl group would cause **1** to be sufficiently electrophilic for silicate formation.

Once we had obtained the optimal reaction conditions, we explored the scope of the reaction. Various aryl iodides,

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listed in Table 2, were used in the reaction. 4-Isopropyliodobenzene and 1-iodonaphthalene both participated in the reaction to afford the products in good yields (entries 1 and 2). 4-Phenyliodobenzene and 4-benzyloxyiodobenzene retarded the reaction, producing 6d and 6e, respectively, in moderate yields (entries 3 and 4). Although 4-iodothioanisole tolerated the reaction conditions, the reaction time had to be extended to obtain **6f** in moderate vield (entry 5). The reactivity of 3-iodo-9-phenylcarbazole 5g was almost the same as that of 4-iodoanisole, producing a good yield of 6g in a short reaction time (entry 6). Substrates 5h and 5i, with ortho alkoxy substituents, could also be used in the reaction, although the reaction time was longer as a result of steric hindrance around the reaction site. In the case of substrates with an electron-withdrawing group, the yields were suppressed even with prolonged reaction times. 4-Ethoxycarbonyl-substituted iodobenzene 5j was converted to **6i** in acceptable yields. *N*-Boc-protected aniline derivatives did not participate in the reaction, and strongly electron-withdrawing nitro substituents also hindered the reaction. To investigate the compatibility of aryl bromides with the reaction, 4-bromoanisole was used as the substrate.

The reaction was unsuccessful and resulted in only the low conversion of **5m** to **6a** (entry 12).

In summary, we synthesized 1 for use in a new strategy for easy access to  $\beta$ -trifluoromethylstyrene derivatives via Hiyama cross-coupling reactions with aryl iodides. The synthetic protocol required commercially available materials, gave good yields (74% over three steps), and was applicable to gram-scale syntheses. In particular, 1 participated in Hiyama cross-coupling reactions with aryl iodide in the presence of CsF, without the need for any special equipment. Palladium ligated with the bulky trimesitylphosphine ligand catalyzed the reaction effectively, producing a variety of  $\beta$ -trifluoromethylstyrenes. Further refinement of the reaction conditions to make the reaction compatible with substrates with electron-withdrawing substituents is now underway.

**Supporting Information Available.** Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.