Preliminary Note

Synthesis of trifluoromethyl-substituted conjugated enynes including a fluorinated siccayne

Chang-Ming Hu*, Feng Hong and Yuan-Yao Xu

Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032 (People's Republic of China)

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Abstract

Trifluoromethyl-substituted conjugated enynes have been synthesized in good to excellent yield through palladium-catalyzed condensations of 2-bromo-3,3,3-trifluoropropene with 1-alkynes. A novel fluorinated siccayne has been prepared by this methodology.

Methods for the synthesis of fluorine-containing compounds have received a growing interest in recent years, as such compounds usually exhibit certain biological activity [1]. Several kinds of fluorinated dienes [2] and enynes [3] have been synthesized via the palladium-catalyzed reaction of halofluoroalkenes with organozinc compounds or direct palladium-catalyzed coupling of halofluoroalkenes with 1-alkynes [4]. We have recently described an access to trifluoromethyl-substituted dienes via palladium-catalyzed cross-coupling reactions of haloalkenes with a 2-bromo-3,3,3-trifluoropropenyl zinc reagent [5]. However, to our knowledge, a method for the preparation of conjugated enynes containing CF_3 groups has not been described hitherto, although such compounds are useful intermediates for synthesizing CF_3-substituted biologically active compounds [6]. Thus, it seems desirable to search for an effective method for the synthesis of such conjugated CF_3-containing enynes. Herein, we wish to report a convenient method for the synthesis of such enynes (**3**) via the direct palladium-catalyzed condensations of 2-bromo-3,3,3-trifluoropropene (**1**) with 1-alkynes (**2**) (Scheme 1). The synthesis of a fluorinated siccayne, 4-(2,5-dihydroxyphenyl)-2-trifluoromethyl-1-buten-3-yne has been accomplished using this methodology.

We have found that the direct coupling of 2-bromo-3,3,3-trifluoropropene (**1**) with 1-alkynes (**2**) proceeds readily in the presence of bis(triphenyl-

*To whom all correspondence should be addressed.

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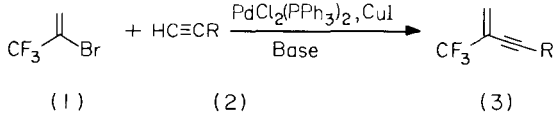


(1) (2) (3)

Scheme 1. Synthesis of CF_3-containing conjugated enynes.

TABLE 1

Palladium-catalyzed coupling of 2-bromo-3,3,3-trifluoropropene (**1**) with 1-alkynes (**2**)

Entry No.	1-Alkyne	Procedure[a]	Time (h)	Product (**3**)	Yield[b] (%)
	R=				
1	Ph (**2a**)	A	5	**3a**	90
2	$HOCH_2$ (**2b**)	A	8	**3b**	80
3	$THPOCH_2$ (**2c**)	A	6	**3c**	85
4	$THPO(CH_2)_6$ (**2d**)	A	8	**3d**	80
5	$THPO(CH_2)_8$ (**2e**)	A	10	**3e**	75
6	$CH_3(CH_2)_2$ (**2f**)	B	4	**3f**	80
7	$CH_3(CH_2)_4$ (**2g**)	B	6	**3g**	75

[a]A: Reactions were carried out in THF (15 ml) at r.t. with $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), Et_3N (30 mmol), **1** (10 mmol) and **2** (12 mmol) under argon. B: Reactions were carried out in Bu^n_3N (20 ml) at 60 °C with $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), **1** (10 mmol) and **2** (12 mmol) under argon.

[b]Isolated yield. All products gave satisfactory spectral and microanalytical data.

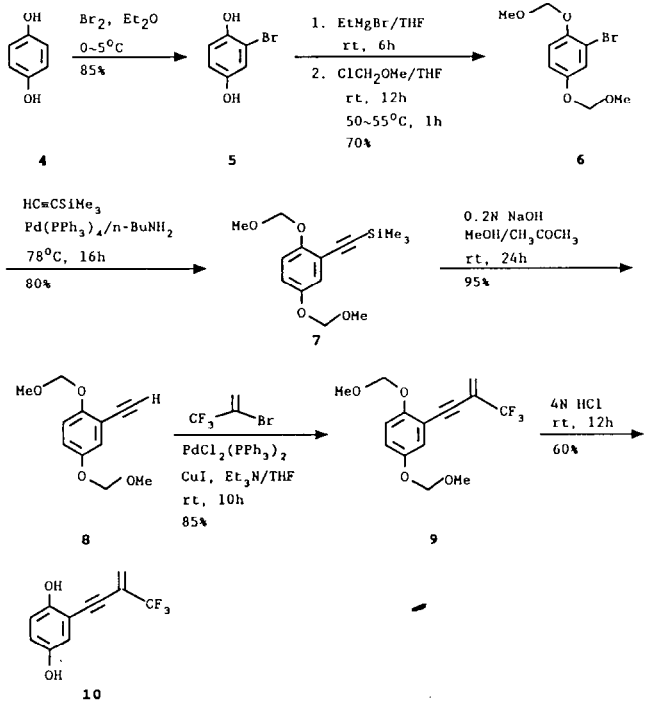
phosphine)palladium dichloride and cuprous iodide, plus a suitable base, to afford in good yield the desired conjugated enynes **3** containing the CF_3 group. The results obtained are summarized in Table 1.

This direct coupling reaction may be illustrated by two typical experimental procedures. **Procedure A** (marked A in Table 1): A two necked-flask fitted with a septum, stir bar and condenser topped with a nitrogen inlet was charged with 0.1 g (2 mol%) of $Pd(PPh_3)_2Cl_2$, 0.05 g (4 mol%) of CuI, 4.8 ml (30 mmol) of Et_3N and 15 ml THF. Then, 1.75 g (10 mmol) of 2-bromo-3,3,3-trifluoropropene [7] and 12 mmol (1.2 equiv.) of 1-alkyne were added to the catalytic mixture via a syringe. The resultant mixture was stirred at room temperature for 4–10 h. The reaction mixture was then poured into 20 ml of 2 N hydrochloric acid and extracted with ether (3×15 ml). The combined ether extracts were washed with brine, dried over Na_2SO_4 and concentrated to give a residue which was subjected to silica gel chromatography. **Procedure B** (marked B in Table 1). All conditions were the same as in Procedure A, except that 20 ml of Bu^n_3N was used instead of Et_3N and THF. The reaction mixture was stirred at 60 °C for 4–6 h. After that, the pure product was obtained by distillation under reduced pressure. Both procedures gave products in good yields.

Siccayne, 4-(2,5-dihydroxyphenyl)-2-methyl-1-buten-3-yne, was first isolated from a culture broth of *Helminthosporium* siccans [6] and later

extracted from submerged cultures of the marine basidiomycete *Halocyphina villosa* [8]. In both cases, the antimicrobial activity of the metabolite was studied and the results showed that siccayne possesses antibiotic properties. Recently, the total synthesis of siccayne has been reported [9]. From the above-mentioned successful coupling of 2-bromo-3,3,3-trifluoropropene with 1-alkynes, we envisioned that a novel 2-CF_3-siccayne could be readily synthesized by this methodology. Thus, hydroquinone (**4**) was first converted into 2-bromohydroquinone (**5**) by bromination. Protection of the phenolic OH by chloromethoxylmethane gave **6**. Coupling of **6** with trimethylsilylacetylene in the presence of palladium provided **7**. Desilylation, followed by coupling with 2-bromo-3,3,3-trifluoropropene gave **9**. Finally, the protective group was removed to afford the new fluorinated siccayne **10*** (Scheme 2).

In summary, we have studied the palladium-catalyzed condensation of 2-bromo-3,3,3-trifluoropropene with 1-alkynes and established an attractive route for the preparation of trifluoromethyl-substituted enynes: a fluorinated siccayne has been synthesized using this methodology.



Scheme 2. Synthesis of fluorinated siccayne.

*Spectroscopic data for **10**: ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ: 6.21 (m, 2H, $=CH_2$); 7.1 (m, 3H arom.) ppm. ^{19}F NMR (60 MHz, $(CD_3)_2CO$) δ: -9.5 (s, CF_3) ppm. IR (KBr) (cm^{-1}): 3500–3200; 2200; 1610; 1120. MS (*m/e*): 228 (M^+); 159. HRMS: calc. for $C_{11}H_7F_3O_2$, 228.0396. Found: 228.0420.

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