

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)

(Received September 28, 1992; accepted December 2, 1992)

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 haloalkenes with organozinc compounds or direct palladium-catalyzed coupling of haloalkenes 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.

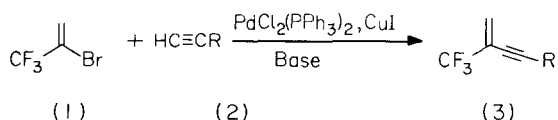
Scheme 1. Synthesis of CF₃-containing conjugated enynes.

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

^aA: Reactions were carried out in THF (15 ml) at r.t. with PdCl₂(PPh₃)₂ (2 mol%), CuI (4 mol%), Et₃N (30 mmol), **1** (10 mmol) and **2** (12 mmol) under argon. B: Reactions were carried out in Bu₃N (20 ml) at 60 °C with PdCl₂(PPh₃)₂ (2 mol%), CuI (4 mol%), **1** (10 mmol) and **2** (12 mmol) under argon.

^bIsolated yield. All products gave satisfactory spectral and microanalytical data.

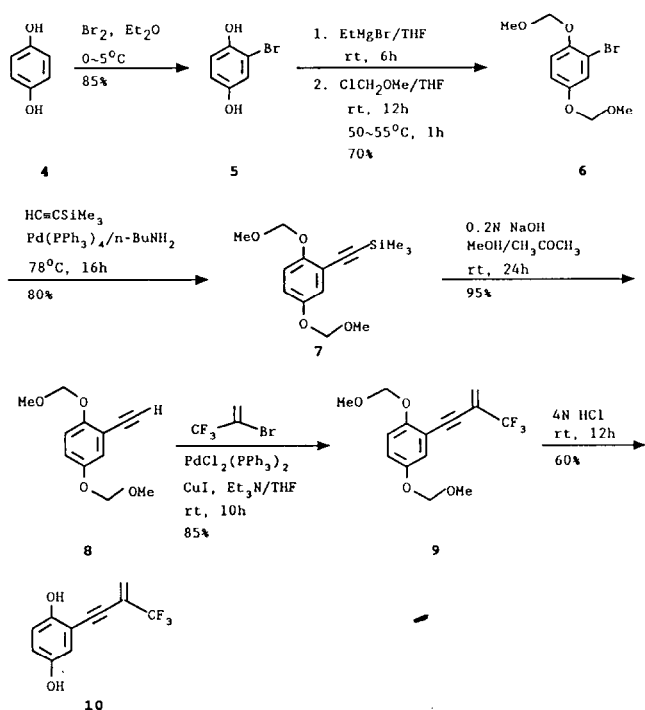
phosphine)palladium dichloride and cuprous iodide, plus a suitable base, to afford in good yield the desired conjugated enynes **3** containing the CF₃ group. The results obtained are summarized in Table 1.

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(PPh₃)₂Cl₂, 0.05 g (4 mol%) of CuI, 4.8 ml (30 mmol) of Et₃N 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 Na₂SO₄ 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 Bu₃N was used instead of Et₃N 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-CF₃-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 chloromethoxymethane 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**: ¹H NMR (200 MHz, (CD₃)₂CO) δ: 6.21 (m, 2H, =CH₂); 7.1 (m, 3H arom.) ppm. ¹⁹F NMR (60 MHz, (CD₃)₂CO) δ: -9.5 (s, CF₃) ppm. IR (KBr) (cm⁻¹): 3500–3200; 2200; 1610; 1120. MS (*m/e*): 228 (M⁺); 159. HRMS: calc. for C₁₁H₇F₃O₂, 228.0396. Found: 228.0420.

Acknowledgment

We gratefully acknowledge financial support from the National Natural Science Foundation of China and from Academia Sinica.

References

- 1 J.T. Welch, *Tetrahedron*, **43** (1987) 3123.
- 2 F. Teiller, R. Sauvetre and J.F. Normant, *J. Organomet. Chem.*, **364** (1989) 17; *ibid.*, 292 (1985) 19; *ibid.*, **303** (1986) 309.
- 3 F. Teiller, R. Sauvetre and J.F. Normant, *Tetrahedron Lett.*, **27** (1986) 3147; Z.-Y. Yang and D.J. Burton, *Tetrahedron Lett.*, **31** (1990) 1369.
- 4 S. Eddarir, H. Mestdagh and C. Rolando, *Tetrahedron Lett.*, **32** (1991) 69; Z.-Y. Yang and D.J. Burton, *J. Fluorine Chem.*, **52** (1991) 443; Z.-Y. Yang and D.J. Burton, *Tetrahedron Lett.*, **31** (1990) 1639.
- 5 B. Jiang and Y.-Y. Xu, *Tetrahedron Lett.*, **32** (1992) 511.
- 6 K. Ishibashi, T. Shindo, M. Arai and H. Mishima, *Sankyo Kenkyusho Nempo*, **20** (1968) 76; *Chem. Abs.*, **71** (1969) 38 498.
- 7 A.L. Henne and M. Nager, *J. Am. Chem. Soc.*, **73** (1951) 1042.
- 8 J.M. Kupka, G. Tsoupras and R. Tabacchi, *Helv. Chim. Acta*, **72** (1989) 929.
- 9 M. Pinault, Y. Frangin, J.-P. Genet and H. Zamarlik, *Synthesis*, (1990) 935.