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Ethyl 3-Iodo-4,4,4-Trifluoro-2(Z)-Butenoate: Regio- and Stereo-Specific Preparation and Palladium-Catalyzed Reaction with Terminal Alkynes

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Abstract Ethyl 3-iodo-4,4,4-trifluoro-2(Z)-butenoate (2) was regio- and stereospecific prepared from ethyl 4,4,4-trifluoro-2-butynote (1). The Sonogashira reaction of 2 with terminal alkynes afforded the (2Z)-en-4-ynoic acid derivatives containing trifluoromethyl group (4). © 1997 Elsevier Science Ltd.

Trifluoromethylated organic molecules often confer significant changes in their chemical and physical properties, and therefore methods for the synthesis of trifluoromethylated compounds received a growing interest in recent years. ¹ Trifluoromethylation² and halogen-exchange reaction³ are possible methods for constructing trifluoromethylated compounds, but these suffer from low reactivity and low selectivity. An alternative approach is the preparation and application of trifluoromethylated building blocks.⁴ We described herein the regio- and stereo-specific preparation of ethyl 3-iodo-4,4,4-trifluoro-2(z)-butenoate (2), a novel trifluoromethylated building block, and its application as a partner in the Sonogashira reaction.

Several years ago, Lu et al ⁵ reported the nucleophilic hydrohalogenation of 2-alkynoic acids by heating with lithium halides in HOAc. Based on Lu's procedure, We were delighted to observe that the reaction of 1 with sodium iodide in acetic acid afforded 2 as sole product in 75% isolated yield (eq. 1).⁶ Although the trifluoromethyl group possesses powerful electron-withdrawing ability,⁷ the iodide ion attacks at the β -position of the carbonyl group and the resulting reaction implied that trifluoromethyl group plays no role in nucleophilic hydrohalogenation of 1. Because compound 1 is highly volatile, the reaction was carried out in a sealed tube. The starting material 1 was easily prepared from α -acylmethylenephosphorane.⁸ This method

offers a novel process for synthesizing such trifluoromethylated building blocks. The configuration of trisubstituted double bond in 2 was assigned by ¹⁹F NMR spectroscopy (δ_F (using CF₃CO₂H as external standard, upfield positive): -10.0 ppm for trifluoromethyl group in 2): δ_F values for the CF₃ group in the 4,4,4-trifluoro-2-butenoates were close to -10.0 ppm which is diagnostic for the CF₃ group and CO₂C₂H₅ group being *trans* oriented.⁹



2 is a valuable building block in the synthesis of compounds containing the trifluoromethyl group because three functional groups are present: the C-I bond, the conjugated C=C bond, and the carbonyl group. To demonstrate the synthetic utilities of 2, the palladium-catalyzed reaction of 2 with terminal alkynes was investigated. ¹⁰ Reaction of 2 with terminal alkyne 3 in the presence of PdCl₂(PPh₃)₂ and CuI in triethylamine at room temperature afforded conjugated (2Z)-en-4-ynoic acid derivatives containing trifluoromethyl group (4) in high yield (eq. 2). The results are summarized in Table 1. In the case of *p*methoxytetrafluorophenylacetylene (Table 1, entry 1d), an exceptionally longer reaction time (72 h) was necessary to complete the Sonogashira reaction. the configuration of double bonds remained intact. Stereodefined conjugated 2-en-4-ynoic acid derivatives represent a class of important synthetic intermediates ¹¹ and a wide variety of natural products of biological interest. ¹² The method described here provides a convenient and practical route to (2Z)-en-4-ynoic acid derivatives bearing a trifluoromethyl group.



We are currently trying to apply these developed procedures to the highly stereoselective synthesis of retinoids bearing trifluoromethyl groups.

Experimental procedure for the preparation of 2: A mixture of ethyl 4,4,4-trifluoro-2-butynote (4.0 g, 24 mmol), NaI (4.5 g, 30 mmol) and HOAc (12 ml) was placed in a sealed tube. The reaction was carried out with magnetic stirring under nitrogen at 70°C for 72h. Then, water (60 ml) was added, and the mixture was cautiously neutralized with solid potassium carbonate, added in portions. Then the aqueous solution was extracted with ether (3×50 ml), and the organic layer was dried (MgSO₄), concentrated, and flash chromatographed (petroleum ether-ethyl acetate=50:1) to yield 2 (5.3 g, 75%).

Typical experimental procedure for the Sonogashira reaction of 2: To a three-necked, round-bottomed flask were added 2 (360 mg, 1.2 mmol), p-nitrophenylacetylene (200 mg, 1.36 mmol), CuI (13 mg, 0.07 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.03 mmol) and triethyl amine (5 ml) under nitrogen. The reaction mixture was stirred at room temperature for 24 h. Ether (10 ml) and 5% aqueous HCl (10 ml) were added to the flask. The organic layer was washed with brine (2×20 ml), dried (MgSO₄), concentrated, and flash chromatographed (petroleum ether-ethyl acetate=50:1) to yield **4f**¹³(330 mg, **88**%).

entry	R	Time	Products	Isolated Yield	$\delta_F (ppm)^{a}$	δ _{C=CH} (ppm)
		(hr)		%		
la	SiMe ₃	24	4a	76	-10.5	6.65
1b	C ₆ H ₅	24	4b	87	-10.3	6.47
1 c	$(CH_2)_7 CH_3$	24	4c	92	-9.6	6.53
1d	F F F	72	4d	93	-10.5	6.71
1 e	(CH ₂) ₅ CH ₂ OH	24	4e	93	-9.7	6.55
1 f	p-O ₂ NC ₆ H ₄	24	4 f	88	-10.3	6.67
1g	(CH ₂) ₃ CH ₃	24	4g	91	-9.8	6.47
lh	CH ₃ OH CH ₃	24	4h	85	-10.1	6.58

Table 1: Pd-Catalyzed Coupling of Ethyl 3-Iodo-4,4,4-Trifluoro-2(Z)-Butenoate (2) with 1-Alkynes (3)

a). using CF₃CO₂H as an external standard, upfield positive.

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6. Selected date for compound 2. $\nu_{max}/cm^{-1}($ neat): 2988, 1736, 1635, 1369, 1314, 1264, 1194, 1151, 1027, 983, 915, 883, 660; $\delta_{H}(300MHz, CDCl_3)$: 1.27 (t, 3H, $J = 7.0Hz, CH_3$), 4.24(q, 2H, $J=7.0Hz, OCH_2$), 7.08(s, 1H, olefinc H)ppm. $\delta_{F}(56.7MHz, CDCl_3)$: -10.0(s, CF₃)ppm. m/z(EI, 70ev): 294(M⁺, 71), 266(66), 249(100), 221(42), 127(18), 75(25). Anal. Calcd for C₆H₆F₃IO₂: C, 24.50; H. 2.06. Found: C, 24.54; H, 1.88.

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13. Selected date for compound **4f**: $v_{max}/cm^{-1}($ neat):2997, 2208, 1714, 1592, 1523, 1367, 1346, 1310, 1256, 1183, 1148, 1016, 956, 900, 857, 750, 686, 671; $\delta_{H}(300MHz, CDCl_3)$: 1.28(t, 3H, *J*=7.0Hz, CH₃), 4.24(q, 2H, *J*=7.0Hz, OCH₂), 6.67(s, 1H, olefinc H), 7.66(d, 2H, *J*=12.0Hz, Ar H), 8.19(d, 2H, *J*=12.0Hz, Ar H)ppm; $\delta_{F}(56.7MHz, CDCl_3)$: -10.3(s, CF₃)ppm; *m*/*z*(EI, 70ev): 314 (M⁺+1, 100), 313 (M⁺, 78), 297(31), 294(15), 268(31), 248(20), 219(25); Anal. Calcd for C₁₄H₁₀F₃NO₄: C, 53.68; H. 3.22. Found: C, 53.66; H, 3.29.

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