Pergamon

Tetrahedron Letters, Vol. 38, No. 38, pp. 6729-6732, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01538-4

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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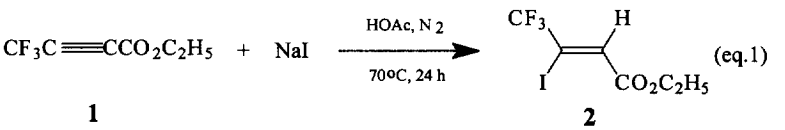
Abstract Ethyl 3-iodo-4,4,4-trifluoro-2(Z)-butenoate (**2**) was regio- and stereo-specific prepared from ethyl 4,4,4-trifluoro-2-butynote (**1**). The Sonogashira reaction of **2** with terminal alkynes afforded the (2Z)-en-4-ynoic acid derivatives containing trifluoromethyl group (**4**). © 1997 Elsevier 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] Trifluoromethylation[2] and halogen-exchange reaction[3] 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.

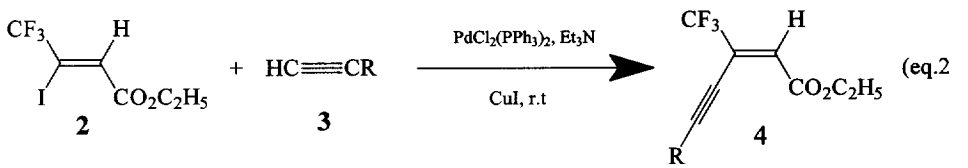
Several years ago, Lu et. al [5] reported the nucleophilic hydrohalogenation of 2-alkynoic acids by heating with lithium halides in HOAc. Based on Lu's procedure, We were delighted to observe that the reaction of **1** with sodium iodide in acetic acid afforded **2** as sole product in 75% isolated yield (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 ^{19}F NMR spectroscopy (δ_F (using CF_3CO_2H as external standard, upfield positive): -10.0 ppm for trifluoromethyl group in **2**): δ_F values for the CF_3 group in the 4,4,4-trifluoro-2-butenoates were close to -10.0 ppm which is diagnostic for the CF_3 group and $CO_2C_2H_5$ group being *trans* oriented.[9]



1 **2**

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 $PdCl_2(PPh_3)_2$ 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.



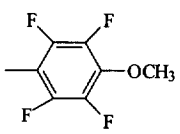
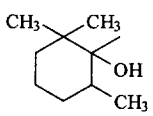
2 **3** **4**

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 ($MgSO_4$), 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 ($MgSO_4$), concentrated, and flash chromatographed (petroleum ether-ethyl acetate=50:1) to yield **4f** [13](330 mg, 88%).

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

entry	R	Time (hr)	Products	Isolated Yield %	δ_F (ppm)[a)]	$\delta_{C=CH}$ (ppm)
1a	$SiMe_3$	24	**4a**	76	-10.5	6.65
1b	C_6H_5	24	**4b**	87	-10.3	6.47
1c	$(CH_2)_7CH_3$	24	**4c**	92	-9.6	6.53
1d		72	**4d**	93	-10.5	6.71
1e	$(CH_2)_5CH_2OH$	24	**4e**	93	-9.7	6.55
1f	p-$O_2NC_6H_4$	24	**4f**	88	-10.3	6.67
1g	$(CH_2)_3CH_3$	24	**4g**	91	-9.8	6.47
1h		24	**4h**	85	-10.1	6.58

a). using CF_3CO_2H as an external standard, upfield positive.

Acknowledgment: We thank National Natural Science Foundation of China, Shanghai Municipal Scientific Committee and the Shanghai Branch, Chinese Academy of Sciences for funding this work.

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6. Selected date for compound **2**. ν_{max}/cm^{-1}(neat): 2988, 1736, 1635, 1369, 1314, 1264, 1194, 1151, 1027, 983, 915, 883, 660; δ_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. δ_F(56.7MHz, $CDCl_3$): -10.0(s, CF_3)ppm. *m/z*(EI, 70ev): 294(M^+, 71), 266(66), 249(100), 221(42), 127(18), 75(25). Anal. Calcd for $C_6H_6F_3IO_2$: C, 24.50; H. 2.06. Found: C, 24.54; H, 1.88.

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13. Selected date for compound **4f**: ν_{max}/cm^{-1}(neat):2997, 2208, 1714, 1592, 1523, 1367, 1346, 1310, 1256, 1183, 1148, 1016, 956, 900, 857, 750, 686, 671; δ_H(300MHz, $CDCl_3$): 1.28(t, 3H, J=7.0Hz, CH_3), 4.24(q, 2H, J=7.0Hz, OCH_2), 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; δ_F(56.7MHz, $CDCl_3$): -10.3(s, CF_3)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 $C_{14}H_{10}F_3NO_4$: C, 53.68; H. 3.22. Found: C, 53.66; H, 3.29.

(*Received in China* 23 *May* 1997; *revised* 11 *June* 1997; *accepted* 4 *July* 1997)