Pergamon

Tetrahedron Letters 40 (1999) 3151–3154

TETRAHEDRON LETTERS

Synthesis of Ethyl (13*E*)-Trifluoromethylretinoate and its Analogues by Palladium-Catalysed Cross-Coupling

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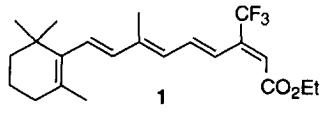
Received 15 December 1998; accepted 19 February 1999

Abstract : Stereoselective construction of ethyl (13*E*)-trifluoromethylretinoate was achieved through two successive Stille reactions. The coupling of (*E*)-1,2-bis(tributylstannyl)ethene and ethyl (*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate was performed first and followed by iododestannylation. The second step involved another vinyltin which was synthetised by stannylmetallation of the Negishi dienyne **4c** derived from β-ionone. Certain yne analogues were also prepared through Sonogashira coupling with **4c,d** and ethyl 5-iodo-3-trifluoromethyl-pent-2,4-dienoate **3**.

keywords: ethyl (13*E*)-trifluoromethylretinoate, Stille reactions, ethyl (*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate, Sonogashira cross-coupling, (*E*)-1,2-bis(tributylstannyl)ethene, stannylmetallation,

Due to their unique physiological and physical properties, trifluoromethylated compounds have been widely used in various fields.[1] Their synthesis has thus become very important in organic and medicinal chemistry.[2,3] However the methodologies available for the preparation of trifluoromethylated compounds are very limited because of the low reactivity of various trifluoromethylated reagents and because of the need for strict experimental conditions. Among these compounds, trifluoromethyl substituted α,β-unsaturated esters and trifluoromethyl substituted polyenes, which are valuable intermediates in synthetic organic chemistry,[4,5] have previously been obtained by Wittig-Horner olefination of trifluoromethyl ketones, from phosphonates[6] or sulphones[7] bearing a trifluoromethyl group. These major routes have been successfully applied to the synthesis of trifluoromethyl-substituted juvenile hormone,[8] retinal[9] or retinoic acid.[10] Nevertheless, the low *E/Z* selectivity of the trisubstituted double bond created constitutes the major drawback of these approaches. We have recently described a new approach for the synthesis of ethyl 3-trifluoromethyldienoate derivatives, with a fixed configuration based on the Stille reaction.[11] Following a similar approach, we now wish to report a stereocontrolled synthesis of ethyl (13*E*)-trifluoromethyl retinoate **1** and some of its analogues.



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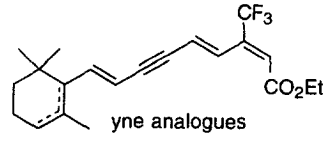

yne analogues

Our retrosynthetic strategy (Scheme **1**) is based on the coupling of two building blocks, **A** and **B**, and starts from the commercially available and inexpensive β–ionone and ethyl 4,4,4-trifluorobut-2-ynoate.

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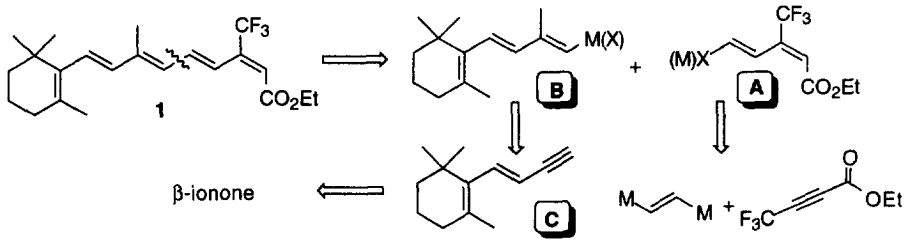
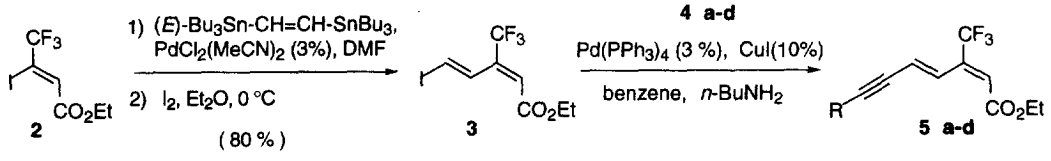
PII: S0040-4039(99)00414-1



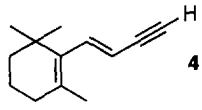
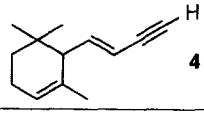
Scheme 1

The construction of fragment A (Scheme 2) began with hydroiodation of ethyl (*Z*)-4,4,4-trifluorobutynoate with a 57% hydroiodic acid solution.[11,12] The pure (*Z*)-vinyliodide **2** underwent Stille coupling with (*E*)-1,2-bis-(tributylstannyl)ethylene (1.2 eq.) in the presence of a catalytic amount (3%) of dichlorobis-(acetonitrile)palladium(II) to provide the corresponding dienyltin in 84% yield with retention of the configuration of both double bonds.[13] Subsequent iododestannylation of the dienyltin adducts in ether at room temperature yielded the pure dienyliodide ester (*E,E*)-**3** (95%).[14]

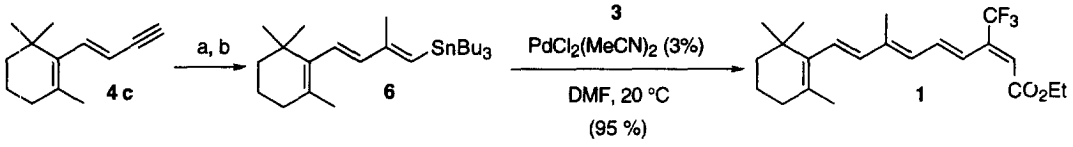


Scheme 2

We first investigated the synthesis of yne analogues of trifluororetinoic acid under Heck-Sonogashira conditions. Different experimental conditions recommended for such cross coupling have already been tested. We found that, with trimethylsilylacetylene or phenylacetylene, the combination of tetrakis(triphenylphosphine) palladium(0), copper iodide and butylamine gave dienynes **5a** and **5b** respectively in fair yields.[15] As already observed,[16] products resulting from the duplication reaction of terminal alkyne were detected in each case leading to the use of a slight excess of alkyne. Extending this procedure to enynes derived from β- or α-ionone (obtained in 75-80% yield according to the Negishi procedure[17]), the expected trifluororetinoids **5c** and **5d** were obtained with retention of configuration of the double bond.[18] it should be noted that, using enyne **4d** (entry 4), the conjugated product **5c** was not detected.

entry	4		5	Yield (%)
1	$Me_3Si-\equiv-H$	**4a**	**5a**	48
2	$Ph-\equiv-H$	**4b**	**5b**	75
3		**4c**	**5c**	64
4		**4d**	**5d**	66

Attention was next directed to the synthesis of ethyl (13*E*)-trifluoromethylretinoate. The synthesis of fragment **B** (Scheme 3) began with stannylcupration of dienyne **4c**.[19] Treatment of **4c** with 1.1 equivalent of lithium butyltributylstannylcyanocuprate (Lipshutz reagent) at -90 °C yielded the intermediate vinylcuprate which was trapped with an excess of methyl iodide (10 eq.) in the presence of HMPA (4 eq.) to afford (7*E*,9*E*)-dienylstannane **6** mixed with a small amount of the internal vinylstannane (terminal/internal = 92/8).[20]



i) $Bu_3SnCu(Bu)CNLi_2$, THF, - 90 °C; ii) HMPA (4 eq.), -90 ° C, 5 mn then MeI (10 eq.), -90 °C to 25°C, 12h (78%)

Scheme 3

Finally, Stille cross-coupling[21] of **6** with **3** gave the desired ethyl (13*E*)-trifluoromethylretinoate **1** in 95 % yield[22] in the presence of a catalytic amount of dichlorobis(acetonitrile)palladium(II) (3%). It is interesting to note that, starting from the mixture of vinylstannanes **6** and its internal isomer, only the terminal regioisomer led to the desired coupling product.

In conclusion, an efficient and concise synthesis to geometrically pure ethyl (13*E*)-trifluoromethylretinoate and some of its analogues was achieved in fair overall yields (40-55 %, 4 steps) from ethyl (*Z*)-4,4,4-trifluorobutynoate and inexpensive ionones.

Acknowledgements: We thank the CNRS and MESR for providing financial support and the "Service d'analyse chimique du vivant de Tours" for recording NMR and mass spectra.

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18. Preparation of **5c** : 237 mg (3% mol) of tetrakistriphenylphosphinepalladium(0) were added to a stirred benzene solution (80 mL) of alkyne **4d** (6.87 mmol) and 0.68 mL of *n*-butylamine then after 5mn, 1 g (3.15 mmol) of **3** and 30 mg (0.16 mmol) of cuprous iodide were added to the solution. The mixture was stirred for 12h at room temperature then hydrolysed with a saturated ammonium chloride solution (30 mL). After usual work-up the crude product was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2: 90/10) ; IR (cm^{-1}) : 3080, 2175, 1723, 1620, 1574; ^{1}H NMR (200 MHz) ($CDCl_3$) δ(ppm): 1.07 (6H, s), 1.35 (3H, t, *J* = 7.1Hz), 1.45-1.67 (4H, m), 1.77 (3H, s), 2.06 (2H, bt, *J* = 6.1Hz), 4.28 (2H, q, *J* = 7.1Hz), 5.69 (1H, dd, *J* = 16.3Hz, *J* = 2.3Hz), 5.76 (1H, s), 6.38 (1H, d, *J* = 16.8Hz), 6.74 (1H, d, *J* = 16.3Hz), 7.82 (1H, d, *J* = 16.8Hz).^{13}C NMR (50.3 MHz) ($CDCl_3$) δ(ppm): 13.9 , 18.9, 21.5, 28.6, 33.2, 33.9, 39.5, 61.0, 89.0, 97.7, 111.3, 119.1, 120.0 (q, $^{3}J_{C\text{-}F}$ = 6Hz), 122.2 (q, $^{1}J_{C\text{-}F}$ = 277Hz), 128.8, 132.8, 136.9, 139.5 (q, $^{2}J_{C\text{-}F}$ = 30Hz), 143.0 , 164.2 .^{19}F NMR δ (ppm) (183.3 MHz, $CDCl_3$) (using CF_3COOH as external standard, upfield positive): 9.75 (q, $^{4}J_{H\text{-}F}$ = 1.3Hz); MS (70 eV): m/z = 366 (M, 18), 351(13), 305(26), 278(11), 277(41), 251(23), 249(10), 237(14), 223(24), 183(10), 171(10), 165(15), 153(13), 152(10), 146(12), 145(16), 143(10), 141(13), 131(14), 129(16), 128(16), 119(14), 115(23), 91(33), 69(71), 55(49), 43(70), 41(100).
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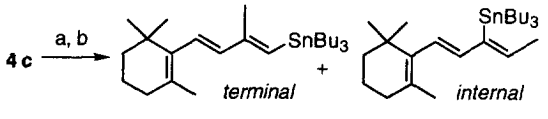

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22. Spectroscopic data of **1** are in agreement with those reported in the literature (ref 10b).