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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Masataka Aoyama , Shoji Hara & Akira Suzuki (1992) BF 3 Etherate Mediated 1,4-Addition Reaction of (1-Alkenyl)dialkoxyboranes to α -Acyl- α , β -unsaturated Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:17, 2563-2569, DOI: 10.1080/00397919208021652

To link to this article: http://dx.doi.org/10.1080/00397919208021652

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BF $_3$ ETHERATE MEDIATED 1,4-ADDITION REACTION OF (1-ALKENYL)DIALKOXYBORANES TO α -ACYL- α , β -UNSATURATED ESTERS

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Abstract: In the presence of BF₃ etherate, (1-alkenyl)dialkoxyboranes react with α -acyl- α , β -unsaturated esters to give α -acyl- γ , δ -unsaturated esters in good yields.

For the carbon-carbon bond formation, 1,4-addition of organometallic compounds to α,β -unsaturated ketones is one of the most efficient methods, among which the use of 1-alkenylborane derivatives for the synthesis of γ,δ -unsaturated ketones is convenient and practical because they can be prepared regio- and stereoselectively by the hydroboration reaction or haloboration reaction of alkynes, and add to α,β -unsaturated ketones without any formation of undesired 1,2-addition products. Recently we reported that (1-alkenyl)-dialkoxyboranes (1) react with α,β -unsaturated ketones in the presence of BF₃ etherate to give γ,δ -unsaturated ketones (2) stereoselectively (eq. 1).

However, other α,β -unsaturated carbonyl compounds such as unsaturated esters never react with 1 under the same or modified conditions. During the course of study on the 1,4-addition reaction of 1 with unsaturated carbonyl compounds, we found that α,β -unsaturated esters (4) having acyl group at the α -position react with 1 to give α -acyl- γ,δ -unsaturated esters (5) in good yields (eq. 2).

1 +
$$R^3$$
 COOEt R^4 COOEt R^4 COOEt R^2 COOEt R^4

The reaction was carried out in the presence of BF₃ etherate³ at 40 °C for 1-3 days. The resulting β -ketoesters (5) have been used for the synthesis of many valuable compounds such as ketones,⁴ esters,⁵ and heterocyclic compounds.⁶ In order to indicate the usefulness of this reaction, γ , δ -unsaturated ketone (6) and α -methylene- γ , δ -unsaturated ester (7) were prepared from 5a (Scheme 1).

Scheme 1

Table 1. Synt	hesis of α-Acyl-γ,	δ-unsaturat	ted Esters (5)
Borane (1)	Ketone (4)ª	React. time (h)	Product (5) ^b Yield, % ^c
Bu B(OPr-i) ₂	COOE	2 4	Bu COOEt 73
	O Pr Et COOE	24	Bu COOEt 70
	Ph	48	Bu COOEt 93
Ph B(OPr-i) ₂	Ph COOE	72	Ph COOEt 74
Br B(OPr-i)2	Ph. COOEs	48	COOE: 75
Bu B(OPr-i) ₂	COOE	24	Bu COOEt 80
Hex B(OPr-i)2	COOE	7 2	Hex COOEt 60

a. A mixture of (E)- and (Z)-isomers was used.

b. A mixture of syn- and anti-isomers.

c. Isolated yield based on the organoborane used.

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568-5.38 (m, 1H), 4.32-4.02 (m, 2H), 3.49-3.25 (m, 2H) 2.38 (t, 6.9 Hz, 2H), 2.22 (s, 1.5H), 2.19 (s, 1.5H), 1.71 5.68-5.35 (m, 1H), 4.32-4.02 (m, 2H), 3.56-3.17 (m, 2H) 2.24.02 (m, 2H), 2.24.02 (m, 2H), 2.25 (s, 1.5H), 2.05 (s, 1.5H), 1.61-0. 2.52-2.22 (m, 2H), 2.25 (s, 1.5H), 2.05 (s, 1.5H), 1.61-0. 2.52-2.22 (m, 2H), 2.25 (s, 1.5H), 2.05 (s, 1.5H), 2.05 (m, 3H), 2.39-3.77 (m, 3H), 2.39-2.03 (m, 3H), 1.39-0.82 (m, 3H) 4.35-3.77 (m, 3H), 2.84-2.23 (m, 3H), 1.39-0.82 (m, 2H), 4.73 4.28-3.74 (m, 3H), 2.84-2.23 (m, 3H), 2.25 (s, 1.5H), 2.11 (m, 2H), 4.29-3.91 (m, 2H), 4.35-3.11 (m, 2.20 (s, 1.5H), 2.13 (s, 1.5 H), 2.10-1.80 (m, 2H), 1.63 (1.50-1.10 (m, 7H), 1.01-0.88 (m, 6H) 2.05-1.1 (20-1.10 (m, 7H), 1.01-0.88 (m, 6H) 2.05-1.1 (30-2.72 (m, 1H), 2.19 (s, 1.5H), 2.14 (s, 1.5H), 2.05-1.1 (45, 3H), 1.67-1.17 (m, 4H), 1.03 (d, 1 = 7.5 Hz, 3H) 0.92 (t, 1 = 8.75 Hz, 3H) 2.14 (s, 1 = 7.5 Hz, 2H) 2.15 (m, 2H), 3.71-2.88 (m, 1H), 2.71-2.88 (m, 1H), 2.47-2.33 (2.11 (s, 3H), 1.67-1.17 (m, 4H), 1.03 (d, 1 = 7.5 Hz, 2H) 2.17 (m, 2H), 3.21-2.88 (m, 1H), 2.71-2.84 (m, 2H), 3.21-2.84 (m, 2H), 3.21	Compounds	¹ H NMR (CDCl ₃ / TMS), (ppm)	IR,(C=O)(cm ⁻¹)	M. S. (M ⁺)
	8 5	5.68-5.38 (m, 1H), 4.32-4.02 (m, 2H), 3.49-3.25 (m, 2H). 2.38 (t, 6.9 Hz, 2H), 2.22 (s, 1.5H), 2.19 (s, 1.5H), 1.71-0.71 (m,13H)	1735, 1712	320.0805
	S b	5.68-5.35 (m, 1H), 4.32-4.02 (m, 2H), 3.56-3.17 (m, 2H), 2.60-2.34 (m, 4H), 1.75-1.11 (m,11H), 0.81 (t, J = 6.2 Hz, 9H)	1740, 1718	360.1303
	50	7.25 (s, 5H), 5.95-5.73 (m, 1H), 4.72-4.47 (m, 1H), 4.25-3.72 (m, 3H), 2.52-2.22 (m, 2H), 2.25 (s, 1.5H), 2.05 (s, 1.5H), 1.61-0.78 (m, 10 H)	1740	382.0987
	5 0	7.61-7.01 (m, 10H), 6.48-6.22 (m, 1H), 4.89-4.60 (m, 1H), 4.35-3.77 (m, 3H), 2.39-2.03 (m, 3H), 1.39-0.82 (m, 3H)	1720	402.0656
	0 0	7.22 (s, 5H), 5.97-5.41 (m, 2H), 5.10-4.80 (m, 2H), 4.73-4.39 (m, 1H), 4.28-3.74 (m, 3H), 2.58-2.26 (m, 4H), 2.25 (s, 1.5H), 2.05 (s, 1.5H), 1.24 (t, 1 = 6.8 Hz, 1.5 H), 1.00 (t, 1 = 6.8 Hz, 1.5 H)	1715	380.0827
	5	4.86 (t, J = 6.8 Hz, 1H), 4.29-3.91 (m, 2H), 3.31-3.11 (m, 2H), 2.20 (s, 1.5H), 2.13 (s, 1.5 H), 2.10-1.80 (m, 2H), 1.63 (s, 3H), 1.50-1.10 (m, 7H), 1.01-0.88 (m, 6H)	1718	254.1908
	8	5.67-5.00 (m, 2H), 4.35-3.94 (m, 2H), 3.28 (d, J = 8.75 Hz, 1H), 3.08-2.72 (m, 1H), 2.19 (s, 1.5H), 2.14 (s, 1.5H), 2.05-1.66 (m, 2H), 1.42-1.08 (m, 11H), 1.08-0.71 (m, 6H)	1745, 1718	268.2051
	ဖ	5.44 (d, J = 8.75 Hz, 1H), 3.27-2.88 (m, 1H), 2.47-2.33 (m, 4H), 2.14 (s, 3H), 1.67-1.17 (m, 4H), 1.03 (d, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H)	1720	248.0596
2.41 (t, J = 7.3 Hz, 2H), 1.70-1.11 (m, 10H), 0.61 (t, J =	7	6.11 (s, 1H), 5.71-5.47 (m, 2H), 4.19 (q, J = 6.2 Hz, 2H), 3.71 (m, 1H), 2.41 (t, J = 7.5 Hz, 2H), 1.70-1.11 (m, 10H), 0.81 (t, J = 6.2 Hz, 3H)	1720	288.0704

The reaction was found to proceed without any isomerization of the double bond and the stereochemistry of 1 was demonstrated to be kept in 5. However, the syn- and anti- isomers were always formed in almost 1:1 ratio and the ratio is not dependent on the stereochemistry of 4 used. Even when a pure (E)- or (Z)-isomer of 4 was used, both isomers of 5 were formed in a same ratio. The representative results are shown in Table 1.

Experimental

Materials: (1-Octenyl)diisopropoxyborane,⁷ (2-bromo-1-alkenyl)diisopropoxyboranes,² and (E)-(2-methyl-1-hexenyl)diisopropoxyborane² were prepared according to the literatures. α -Acyl- α , β -unsaturated esters were prepared from the corresponding β -ketoesters and aldehydes according to the literature.⁸

General procedure for the preparation of α -acyl- γ , δ -unsaturated esters

A mixture of (Z)-(2-bromo-1-hexenyl)diisopropoxyborane (0.291 g, 1 mmol), ethyl 2-acetyl-2-butenoate (0.156 g, 1 mmol), and BF₃ etherate (0.142 g, 1 mmol) in 5 mL of CH_2Cl_2 was stirred under reflux for 2 days. After extraction with ether, ethyl (Z)-2-acetyl-5-bromo-3-methyl-4-nonenate (5a) was isolated by preparative tlc (silicagel / benzene : hexane = 9:1) in 75 % yield (0.240 g).

Preparation of 6

In an ethanolic solution of KOH (15 mL of 0.5 M solution), **5a** (0.319 g, 1 mmol) was stirred at room temperature and the reaction was monitored by tlc.

After 3 days, the consumption of **5a** was confirmed and the reaction mixture was acidified by addition of 3M HCl. After extraction with ether, **6** was isolated by preparative tlc (silica gel / benzene: hexane = 9:1) in 98 % yield (0.242 g).

Preparation of 75a

A THF solution of LDA was prepared by addition of a hexane solution of BuLi (0.75 mL of 1.6 M solution, 1.2 mmol) to a THF solution (5 ml) of diisopropylamine (0.121 g, 1.2 mmol) at -78 °C. After 30 min, a THF solution (1 mL) of **5a** (0.319 g, 1 mmol) was added to give a clear yellow solution. The mixture was stirred at -78 °C for 1h and then paraldehyde (0.07 g, 2.3 mmol) was added. Then the cooling bath was removed and the mixture was stirred under reflux for 2h. After extraction with ether, **7** was isolated by preparative tlc (silica gel / benzene: hexane = 9:1) in 71 % yield (0.2 g).

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(Received in USA 29 April, 1992)