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Journal of Fluorine Chemistry 83 (1997) 87–88

JOURNAL OF FLUORINE CHEMISTRY

Preliminary note

Reformatsky reactions of ethyl 4,4-difluoro-3-ethoxy-4-halocrotonates: synthesis of 4,4-difluorocarbonate derivatives and 2-lactenones

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Received 25 November 1996; revised 4 February 1997; accepted 6 February 1997

Abstract

Ethyl 4,4-difluoro-3-ethoxy-4-halocrotonates react with carbonyl compounds in the presence of zinc, giving 4,4-difluorocrotonate derivatives in good yields. A prolonged reaction time results in the formation of 4,4-difluoro-2-lactenones. © 1997 Elsevier Science S.A.

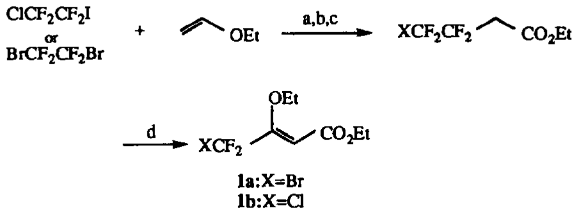
Keywords: Difluorocrotonate; 2-Lactenones; Reformatsky reaction

1. Introduction

In recent years, the introduction of the difluoromethylene fragment into organic compounds has proved to be attractive, as such molecules can inhibit one or more enzymes or can be partially metabolized into more bioactive substances [1]. Halodifluoroacetates, chlorodifluoromethyl ketones and bromodifluoromethyl acetylene [2] are widely used as reagents to introduce a CF_2 moiety into molecules. Reformatsky reactions of 4-chloro-4,4-difluorocrotonate with aldehydes have been reported recently by Tsukamoto and Kitazume [3] and only α-mode products were obtained. In the search for new CF_2-containing synthons, we have found that ethyl 4,4-difluoro-3-ethoxy-4-halocrotonates (**1**) react readily with carbonyl compounds in the presence of zinc powder, giving γ-mode products. Herein, we report our preliminary results.

2. Results

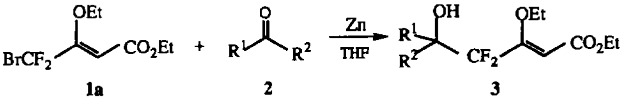
Ethyl 4,4-difluoro-3-ethoxy-4-halocrotonates (**1**) [4] were prepared by a four-step procedure in nearly 50% yield (Scheme 1).



a: $Na_2S_2O_4/NaHCO_3$; b: $K_2Cr_2O_7/H_2SO_4$; c: $EtOH/H^+$; d: $EtOH/Na_2CO_3/CH_2Cl_2$

Scheme 1.

In the presence of zinc powder, **1a** reacts with carbonyl compounds. Such a synthesis is illustrated with PhCHO as an example. In a typical procedure, **1a** (5 mmol) and PhCHO (6 mmol) were mixed with Zn powder (7.5 mmol) in 4 ml of tetrahydrofuran (THF) under nitrogen. The resulting reaction mixture was stirred at 60 °C for 3 h. The mixture was then poured into an aqueous NH_4Cl solution and extracted with Et_2O (3×10 ml). The ether extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent and flash chromatography gave **3a** in 89% yield (Scheme 2). Compound **3a**: oil; IR ν_{max}: 3450, 1720, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.30 (m, 6H, $2 \times CH_3$), 2.88 (br.s, 1H, OH), 4.18 (m, 4H, $2 \times OCH_3$), 5.08 (dd, $J=20$, 15H$_2$, 1H, $CHCF_2$), 5.88 (s, 1H, C=CH), 7.30 (m, 5H, ArH) ppm; ^{19}F NMR (56.4 MHz, $CDCl_3$, CF_3COOH as standard) δ: 33.0 (dd, $J=270$, 15H$_2$, 1F), 40.0 (dd, $J=270$, 2OH$_2$, 1F) ppm; MS (m/e): 301 ($M^+ + 1$, 14), 283 ($M^+ - OH$, 28), 255 ($M^+ - EtO$, 32), 194 ($M^+ - OH - 2 \times OEt$, 100); analysis: calculated for $C_{15}H_{18}F_2O_4$: C, 59.99%; H, 6.04%; F, 12.65%; found: C, 59.69%; H, 5.55%; F, 12.64%. Similar results (Table 1) were obtained with other carbonyl compounds.



1a **2** **3**

Scheme 2.

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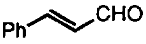
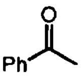
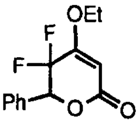
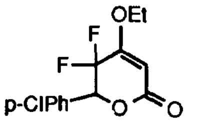
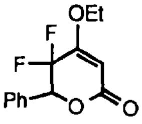
PII S0022-1139(97)00013-4

Table 1
Reaction of **1a** with carbonyl compounds[a]

Entry	1	2	3 (yield)
1	**1a**	PhCHO (**2a**)	**3a** (80%), R^1=Ph, R^2=H
2	**1a**	*p*-ClPhCHO (**2b**)	**3b** (78%), R^1=*p*-ClPh, R^2=H
3	**1a**	*p*-MeOPhCHO (**2c**)	**3c** (85%), R^1=*p*-MeOPh, R^2=H
4	**1a**	 (**2d**)	**3d** (62%), R^1=PhCH=CH, R^2=H
5	**1a**	 (**2e**)	**3e** (70%), R^1=Ph, R^2=CH_3
6	**1a**	C_3H_7CHO (**2f**)	–[b]
7	**1a**	PhCHO (**2a**)	 (**3f**), (65%)[c]
8	**1a**	*p*-ClPhCHO (**2b**)	 (**3g**), (70%)[c]
9	**1b**	PhCHO (**2a**)	 (**3f**), (50%)[d]

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[a] All the reactions were run at 60 °C for 3 h under nitrogen unless indicated otherwise. The molar ratio of **1** : **2** : zinc = 1 : 1.2 : 1.5. The yields were isolated yields. Satisfactory spectral and analytical data were obtained for all new compounds.

[b] Reductive product CF_2=C(OEt)CH_2CO_2Et was obtained.

[c] The reaction was run at 60 °C for 8 h.

[d] The reaction was run at 60 °C for 15 h.

The zinc-promoted reaction proved to be general for carbonyl compounds. When aromatic aldehydes were used as substrates, good yields of 4,4-difluorocrotonate derivatives were obtained independent of the nature of the substituent located at the para position of the aromatic aldehyde. Thus *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde, α,β-unsaturated aldehydes and ketones all reacted well and gave satisfactory results. When an aliphatic aldehyde was used as the substrate, only CF_2=C(OEt)CH_2CO_2Et was obtained.

When the reaction of PhCHO with **1a** was run at 60 °C for 8 h, 4,4-difluoro-3-ethoxy-2-lactenone was obtained in 65% yield (entry 7). *p*-Chlorobenzaldehyde gave a similar result (entry 8).

Ethyl 4-chloro-4,4-difluoro-3-ethoxy crotonate (**1b**) also reacted with aldehyde in the presence of zinc powder, but a longer reaction time was needed and the lactenone was the dominant product.

Although the mechanism of this reaction has not been investigated in detail, relevant work on reactions of XCF_2CF=$CHCO_2Et$ [5] and $ClCF_2CH$=$CHCO_2Et$ [3] with aldehydes has shown that only α-mode products are obtained. In addition, the reaction of **1a** with PhCHO gives the γ-mode product (more than 90%) even when CuCl/Zn and Cp_2TiCl_2/Zn [6] are used as catalysts. This implies that the ethoxy group at the 3-position greatly influences the reactivity and selectivity of **1**. Further investigation is now in progress.

Acknowledgements

We thank the National Natural Science Foundation of China for financial support (No. 296322003).

References

[1] R. Filler, Y. Kobayashi, Biochemical Aspects of Fluorine Chemistry, Elsevier Biomedical Press and Kodansha, Amsterdam, 1982. L.W. Hertel, J.S. Kroin, J.W. Misner, J.M. Tustin, J. Org. Chem. 53 (1988) 2406.
[2] D.J. Burton, Z.Y. Yang, Tetrahedron 48 (1992) 189. Z.Y. Yang, D.J. Burton, J. Org. Chem. 56 (1991) 5125.
[3] K. Tsukamoto, T. Kitazume, Synlett. (1992) 977.
[4] Q.-S. Hu, C.-M. Hu, Chin. J. Chem. in press.
[5] Q.-S. Hu, C.-M. Hu, unpublished results, 1993.
[6] Y. Ding, G. Zhao, J. Chem. Soc., Chem. Commun. (1992) 941.