Synthesis of β,β-difluoroacrylates

Carl L. Bumgardner*, Jason P. Burgess, T. Stephen Everett and Suzanne T. Purrington

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204 (USA)

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Abstract

Diethyl malonates substituted in the α-position by an alkyl group may be bromodifluoromethylated to give derivatives suitable for conversion to β,β-difluoro-α-alkylacrylates. The final step involves dealkoxycarbonylation–elimination promoted by potassium bromide in dimethyl sulfoxide.

Introduction

Routes to β,β-difluoroacrylates ($F_2C{=}CHCO_2R$) are few [1] and preparative methods for β,β-difluoroacrylates substituted in the α-position with an alkyl group are even rarer [2]. Two of these schemes [2a, b] involve the loss of fluoride from α-trifluoromethylacrylate by an S_N2' reaction. The starting acrylate, is derived in several steps from trifluoromethyl acetone, CH_3COCF_3, a relatively expensive starting material [3a, b]. Other methods require an α-keto ester [2c] or a chlorofluoro epoxide [2d] as reactants. So, from the standpoints of convenience, economy and efficiency of fluorine use, the few methods available for β,β-difluoro-α-alkylacrylates are not without drawbacks.

In our development of a synthesis of α-trifluoromethyl esters, $RCH(CF_3)CO_2Et$, from malonates and CF_2Br_2, we postulated that β,β-difluoroacrylates were intermediates; and in one case such a compound was isolated [4]. In view of the paucity of methods for obtaining such acrylates we turned our attention to the possibility of altering our α-trifluoromethyl ester procedure to provide the acrylates in synthetically acceptable yields. Recent reports of the use of β,β-difluoroacrylates in Michael [1] and in Diels–Alder [5] reactions added incentive to the search for α-substituted derivatives. We describe herein some success in developing a new, practical pathway to β,β-difluoroacrylates.

Experimental

General procedures

The ^1H and ^{13}C NMR spectra were obtained on a GE GN-300 NMR spectrometer operating at 300.52 MHz for ^1H and 75.57 MHz for ^{13}C. Spectra

*Author to whom correspondence should be addressed.

were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to internal TMS. ^{19}F NMR spectra were obtained on a Bruker AR-100 spectrometer operating at 95.52 MHz for ^{19}F. Spectra were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to external $CFCl_3$. Negative chemical shifts indicate that the resonances are upfield relative to $CFCl_3$.

Bromodifluoromethyl malonates were prepared according to literature methods. Potassium bromide from Fisher, was flame dried *in vacuo* prior to use. DMSO from Fisher, was twice distilled from CaH_2 *in vacuo* prior to use. Boiling points were determined by a microcapillary method [6] and are reported uncorrected.

Synthesis of ethyl 3,3-difluoro-2-propyl propeneoate (2) (R=Pr)

9.88 g (0.030 mol) of malonate (**3**) (R=Pr) (see Scheme 1), 3.55 g (0.030 mol) of dried KBr and 100 ml of freshly distilled DMSO were combined in a flame-dried three-necked round-bottom flask. The flask was equipped with a magnetic stirrer, a thermometer, a short-path distillation head and a nitrogen inlet. The apparatus was purged with N_2 for several minutes then the nitrogen inlet was removed and replaced with a ground glass stopper. The flask was opened to the atmosphere via a nitric acid bubbler attached to the short-path distillation head. The inhomogeneous mixture was heated quickly to 170 °C with vigorous stirring and maintained at this temperature for the course of the reaction. After several minutes at 170 °C the mixture cleared and developed a red color. The mixture began evolving gases and distillate was collected for approximately 0.5 h until the reaction mixture solidified. At this point the heat source was quickly removed and the reaction vessel immersed in an ice water bath to stop the reaction. During the reaction 6.33 g of a clear colorless distillate (b.p., 130–140 °C) was collected from which a white solid precipitated upon standing. The distillate consisted of a mixture of the acrylate (**2**) (2=Pr), DMSO, methyl sulfide, methyl sulfone and a small amount of acetaldehyde. The solid was removed by filtration and the filtrate distilled under reduced pressure with the volatile materials condensed using a Dry Ice/acetone coldfinger. The material was diluted with cold pentane (5 ml) and flashed through a silica gel plug. The pentane was removed by rotary evaporation to yield 2.63 g (0.0147 mol) of acrylate (**2**) (R=Pr) in >95% purity as estimated by ^1H NMR spectroscopy.

The solid reaction mixture was dissolved in water and extracted with ether. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation to yield 1.80 g (0.00543 mol) of the unreacted malonate.

Yield, 60% (51% conversion based on recovered starting material), b.p., 138 °C. ^1H NMR (δ): 0.90 (t, 3H, $^3J_{HH}=7.3$ Hz); 1.30 (t, 3H, $^3J_{HH}=9.0$ Hz); 2.20 (mult 2H); 4.21 (q, 2H, $^3J_{HH}=7.3$ Hz). ^{13}C NMR (δ): 13.1; 13.9; 21.5; 26.1; 60.8; 88.6 (d of d, $^2J_{CF}=24.4$ Hz, 4.4 Hz); 161.6 (d of d, $^1J_{CF}=293$ Hz, 302 Hz); 165.6. ^{19}F NMR (δ): −72.5 (t, $^4J_{HF}=3.1$ Hz); −78.0 (t, $^4J_{HF}=2.2$ Hz). Analysis: Calcd. for $C_8H_{12}F_2O_2$: C, 53.92; H, 6.79% Found: C, 53.64; H, 6.82%.

The following compounds were prepared by the method described for (**2**) (R=Pr):

Ethyl 3,3-difluoro-2-ethyl propeneoate (2) (R=Me)

Yield, 82% (59% conversion based on recovered starting material), b.p., 94 °C. ^{1}H NMR (δ): 1.25 (t, 3H, $^3J_{HH}$=7.7 Hz); 1.80 (t, 3H, $^4J_{HF}$=3.4 Hz); 4.25 (q, 2H, $^3J_{HH}$=7.7 Hz). ^{13}C NMR (δ): 9.3; 13.9; 61.1; 84.8 (d of d, $^2J_{CF}$=24.4 Hz, 9.8 Hz); 159.9 (d of d, $^1J_{CF}$=293 Hz, 308 Hz); 164.7. ^{19}F NMR (δ): −75.7 (q, $^4J_{HF}$=3.4 Hz); −80.1 (q, $^4J_{HF}$=3.4 Hz). HRMS: Calcd. for $C_6H_8O_2F_2$: MW=150.04924 Found: MW=150.04912.

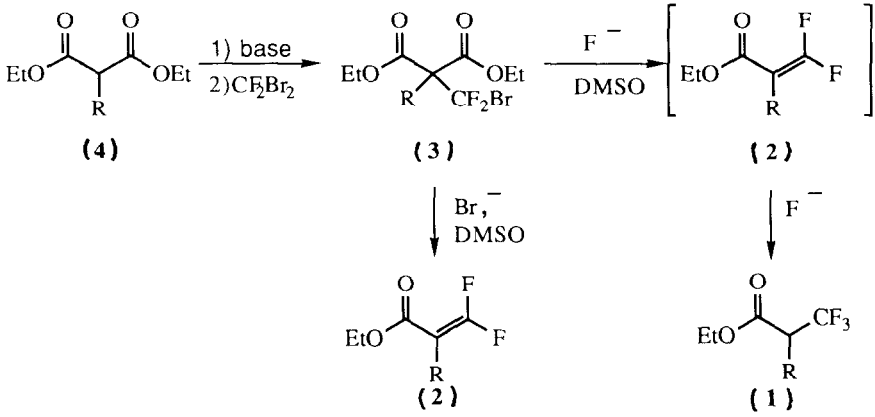
Ethyl 3,3-difluoro-2-ethyl propeneoate (2) (R=Et)

Yield, 52% (45% conversion based on recovered starting material), b.p., 108 °C. ^{1}H NMR (δ): 1.05 (t, 3H, $^3J_{HH}$=7.3 Hz); 1.25 (t, 3H, $^3J_{HH}$=7.3 Hz); 2.20 (mult, 2H); 4.20 (q, 2H, $^3J_{HH}$=7.3 Hz). ^{13}C NMR: (δ) 14.2; 15.0; 18.2; 62.1; 91.5 (d of d, $^2J_{CF}$=24.4 Hz, 4.9 Hz); 161.5 (d of d, $^2J_{CF}$=295 Hz, 308 Hz); 165.0. ^{19}F NMR (δ): −72.5 (t, $^4J_{HF}$=2.2 Hz); −78.5 (t, $^4J_{HF}$=2.9 Hz). Molecular ion: 164.

Results and discussion

Earlier work [4] showed that α-trifluoromethyl esters (**1**) could be prepared via the steps outlined in Scheme 1. In order to make acrylate (**2**) the desired product, instead of ester (**1**), the fluoride ion was replaced with bromide ion and the acrylate (**2**) initially generated was distilled rapidly from the reaction mixture to minimize secondary reactions. Table 1 summarizes the results of treating bromodifluoromethyl malonates (**3**), readily available [4] from malonates (**4**), with KBr in DMSO at 170 °C.

It is necessary to avoid the use of fluoride ion in the procedure since the conversion of (**2**) to (**1**) is very rapid and highly favored thermodynamically.



Scheme 1.

TABLE 1

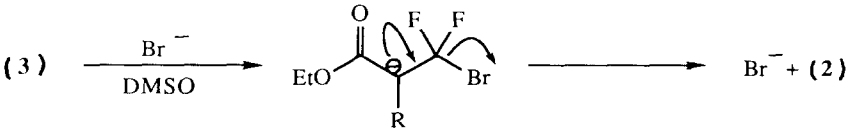
Preparation of $F_2C{=}C(R)CO_2Et$ (2)

R	% yield from (3)[a]	% conversion from (3)	B.p. (°C)	^{19}F NMR spectral data[b]	
				δ (ppm)	J (Hz)
CH_3	82	59	94	−75.7	$^4J_{FH}=3.4$
				−80.1	$^4J_{FH}=3.4$
					$^2J_{FF}=0$
CH_2CH_3	52	45	108	−72.5	$^4J_{FH}=2.2$
				−78.5	$^4J_{FH}=2.9$
					$^2J_{FF}=0$
$CH_2CH_2CH_3$	60	51	138	−72.5	$^4J_{FH}=3.1$
				−78.0	$^4J_{FH}=2.2$
					$^2J_{FF}=0$

[a]Isolated as >95% pure material.

[b]Obtained as an approximately 25 mg ml^{-1} solution in $CDCl_3$ with $CFCl_3$ as an external standard.

The bromide ion was chosen as a substitute for the fluoride ion since there is precedence for bromide-induced dealkoxycarbonylation [4, 7]. In our case, this process presumably leads to anion (**5**) which would be expected to eject bromide and yield acrylate (**2**).



(5)

The ^{19}F spectra (Table 1) reveal an interesting characteristic of α-alkyl-β,β-difluoroacrylates. The geminal fluorine–fluorine coupling constants ($^2J_{FF}$) are zero. This was determined to a resolution of less than 1 Hz. The lack of geminal coupling is in contrast to values recorded for similar systems [1, 2]. A wide range of geminal fluorine coupling constants are possible in this type of unsaturated system and are highly dependent on the electronegativity of the other substituents [8].

In conclusion, a number of β,β-difluoroacrylates (**2**), substituted by alkyl groups in the α-position, can now be obtained in fair to moderate yields from readily available malonates and economical CF_2Br_2 as the source of fluorine atoms. Reactions of these acrylates will be reported in a later communication.

Acknowledgement

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