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Studies on a three-step preparation of β-fluoroalkyl acrylates from fluoroacetic esters

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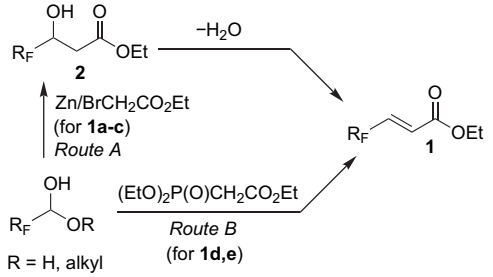
Abstract—β-Fluoroalkyl-acrylic esters are valuable building blocks for the synthesis of organofluorine compounds. Although the preparation of several β-fluoroalkyl-acrylates is known, a general and straightforward lab-scale methodology for the preparation of multigram amounts of these compounds from fluoroacetic esters is not available, and the related chemistry has not been investigated in detail. We now describe an optimized three-step protocol relying on: (1) Claisen-type condensation of fluoroacetic esters with ethyl acetate, using LDA as base; (2) reduction of the resulting γ-fluoro-β-keto esters by $NaBH_4$, using toluene or benzene as solvents; (3) P_2O_5-promoted dehydration of the intermediate γ-fluoro-β-hydroxy esters. The methodology affords preparatively useful yields of the target compounds incorporating only fluorine atoms (CF_3, CHF_2, C_2F_5), whereas the γ-halodifluoromethyl ($CClF_2$, $CBrF_2$, CIF_2) acrylates could not be obtained in analytically pure form from the dehydration step.

1. Introduction

The synthesis of versatile and reactive fluorinated building blocks has remarkable interest, due to the wide range of applications of fluoroorganic compounds in a number of important fields such as drug discovery, materials science, and nanotechnology. Among the vast range of structurally simple and suitably functionalized fluorinated compounds, which can be used as starting building blocks for the synthesis of complex fluorinated molecules, β-fluoroalkyl acrylic acid esters **1** (Scheme 1) are of particular interest.[1] Indeed, their high versatility and reactivity in a number of reactions of remarkable usefulness, such as Diels–Alder and 1,3-dipolar cycloadditions,[2] Friedel–Crafts and Michael-type reactions,[3] dihydroxylation and epoxidation,[4] carboxylate reduction and hydrolysis,[5] and Heck-type reactions,[6] can give access to a wide range of fluorinated analogs of biologically important structures like amino-acids, alkaloids, peptidomimetics, and sugars, just to mention some examples.



R_F = (**a**) CF_3, (**b**) CHF_2, (**c**) C_2F_5, (**d**) $CClF_2$, (**e**) $CBrF_2$, (**f**) CIF_2

Scheme 1. Known preparations of γ-fluoroalkyl-acrylates **1**.

Recently, we became interested in compounds **1a–f** as starting materials for the preparation of fluorinated peptidomimetics and protease inhibitors.[7] Inspection of the literature revealed that there are two main routes to the target compounds, which are all known except for the iodo-derivative **1f** (Scheme 1). The first one (*route A*) is based on the dehydration of the corresponding γ-fluoro-β-hydroxy esters **2**, and has been preferentially used for the preparation of **1a–c**.[8,5b] The intermediate carbinols **2** were generally obtained either by Reformatsky reaction of bromoacetate or by Knoevenagel reaction of malonates with fluoroacetaldehydes or their hemiacetals.

The second (*route B*) relies on the Horner–Wadsworth–Emmons reaction of fluoroacetaldehydes with triethyl phosphonoacetate that was used to prepare **1d**,**e**.[9]

Recent work has also demonstrated the possibility of using Pd-catalyzed Heck-type chemistry, although the yields are currently rather modest.[10] Alternatively, **1a** in pure *Z*-form was obtained by Lindlar-type hydrogenation of CF_3–C≡C–CO_2Et.[11]

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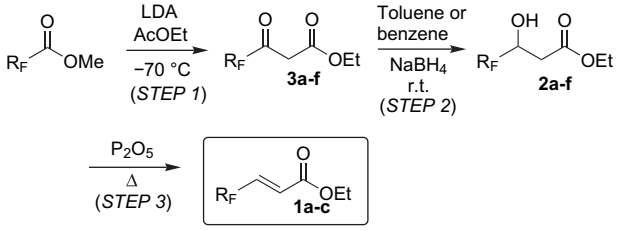
Both routes A and B rely on fluoroacetaldehyde derivatives as starting materials. These compounds are not easily available from commercial sources, except for the trifluoro derivative, and are remarkably expensive. Alternatively, one has to prepare them by reduction of the corresponding esters. Moreover, fluoroacetaldehyde derivatives are somewhat unstable and reactive, particularly in the strongly electrophilic oxo form. We therefore reasoned that the direct use of fluoroacetic esters, which represent by far the cheapest and most readily available starting materials in a wide range of fluorination degrees, would be extremely advantageous, particularly on preparative multigram scale (Scheme 2). Surprisingly, we found that little is published about steps 1 and 2, namely the Claisen-type preparation of γ-fluoro-β-keto esters **3** and their hydride reduction to **2**, which we deemed more suitable for a lab-scale preparation.[12]



R_F = (**a**) CF_3, (**b**) CHF_2, (**c**) C_2F_5, (**d**) $CClF_2$, (**e**) $CBrF_2$, (**f**) ClF_2

Scheme 2. Three-step preparation of β-fluoroalkyl acrylates **1** from fluoroacetates.

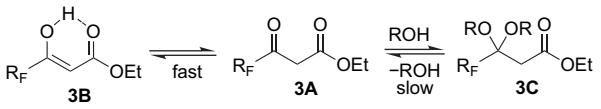
In this paper, we describe the results of a study on the feasibility of a synthesis of β-fluoroalkyl acrylic acid esters (*E*)-**1a–f** in three steps from the corresponding fluoroacetic esters.

2. Results and discussion

Step 1, the preparation of γ-fluoro-β-keto esters **3** from fluoroacetic esters, has been reported to occur under different conditions such as Reformatsky-type (bromoacetate, Zn),[13] or Claisen-type using acetic esters as nucleophiles and EtONa/EtOH,[14] or NaH,[15] or LDA[16] in ethereal solvents as base. In our hands, the latter proved to be by far the best, invariably affording good yields of **3b–f**, generally within the 70–80% range (only **3a** was purchased from commercial sources). These molecules, upon NMR analysis, showed quite complex spectral patterns revealing the presence of three different tautomeric forms often in comparable ratios, depending on the solvent. Although it is known that some γ-fluoro-β-keto esters **3** have a rather peculiar tautomeric distribution, with an unusually high ratio of the β-enol ester form as compared to the unfluorinated counterparts, a detailed study about this aspect is not present, to the best of our knowledge, in the literature.[17] This issue is even more important considering that it is known that the different tautomers of **3a** can have dramatically different reactivity upon reductive conditions.[18] We therefore decided to investigate the tautomeric composition of the whole set of compounds **3a–f** in different solvents, as shown in Table 1.

It should be mentioned that the equilibrium between β-enol ester (**B**) and β-keto ester form (**A**) has been reported to be a fast reaction, and the **A/B** ratio is therefore substantially

Table 1. Tautomeric composition of compounds **3** in different solvents at rt[a,b]



R_F = (**a**) CF_3, (**b**) CHF_2, (**c**) C_2F_5, (**d**) $CClF_2$, (**e**) $CBrF_2$, (**f**) ClF_2

β-Keto ester	$CDCl_3$ (R=H)	C_6D_6 (R=H)	CD_3OD (R=CD_3, D)	Acetone-d_6 (R=H)	DMSO-d_6 (R=H)
3a[d]	10:60:30	11:68:21	2:6:92	28:50:22	27:36:37
3b	33:27:40	36:26:38	8:2:90	33:17:50	15:28:57
3c	11:86:3	9:87:4	9:54:37	24:73:3	23:68:9
3d	25:25:50	15:25:60	5:28:67	21:14:65	20:10:70
3e	30:33:37	32:39:29	n.d.[c]	40:38:22	39:38:23
3f	42:37:21	44:39:17	18:20:62	48:17:35	70:4:26

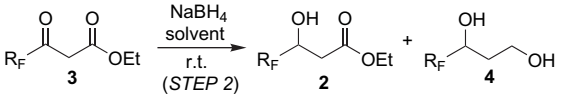
[a] Ratio of compounds **A/B/C**.
[b] The compound was dissolved in a solvent taken from a freshly opened bottle, allowed to stand for 5–10 min, then analyzed by ^{19}F, ^{1}H, and ^{13}C NMR. Little or no variations were observed after longer times, confirming that the equilibrium was actually reached.
[c] The spectrum displayed a very complex pattern with a number of signals, which could not be assigned.
[d] Compound **3a** was reported to have ca. 20:70:10 ratio in THF-d_8 under the same conditions (Ref. 18).

constant for each compound in a given solvent.[17] On the other hand formation of the hemiketal or *gem*-diol form **C** from **A** is a slow process, which is accelerated by the presence of acids or other catalysts, and can be obviously shifted toward **C** by increasing the amount of water. The data portrayed in Table 1 are obtained by ^{1}H, ^{19}F and ^{13}C NMR analysis at rt, by dissolving each compound in the appropriate solvent (freshly opened, untreated) and recording the spectra after 5 min. The data demonstrate that tiny structural differences in γ-position, such as the number of fluorine atoms or a change of halide, are able to bring about strong differences in terms of tautomeric behavior. From the substrate point of view, it clearly appears that the pentafluoroethyl derivative **3c** has a remarkable proclivity to the β-enol ester form **B**, almost independently of the solvent. Less marked prevalence of **B** was determined for the trifluoro compound **3a**. The chlorodifluoro compound **3d** showed a strong preference for the *gem*-diol or hemiketal form **C**, and the same tendency, albeit less pronounced, was evidenced for the difluoro compound **3b**. The tautomeric population of the iododifluoro compound **3f** showed a shift toward the β-keto form **A**, whereas the bromodifluoro **3e** featured a borderline behavior with a general equivalence of population among the three tautomeric forms. In terms of solvent, the trend was that expected and already reported in the literature,[17] namely low-polarity aprotic solvents like benzene favor the intramolecularly hydrogen-bonded tautomer **B**, whereas more polar solvents shift the tautomerism toward the keto form **A**, and methanol favors the formation of the hemiketal form **C**. It is also worth noting that for the halodifluoro compounds **3d–f**, the rate of keto form **A** decreases with increasing the electronegativity of the halogen (Cl>Br>I). Finally, it should be noticed that polar hygroscopic solvents like DMSO and acetone lead to an increase in *gem*-diolic form **C**.

The next transformation (step 2, Scheme 2) was the hydride reduction of the β-keto esters **3** to the carbinols **2**. This reaction is reported only occasionally in the literature, and in some

cases little experimental information was provided.[19,14,15] Ethereal solvents (diethyl ether, THF) or alcohols (MeOH, EtOH), with or without water, are conventionally the most used solvents for the reduction of carbonyl groups with $NaBH_4$, therefore, we explored first the use of diethyl ether and MeOH. Despite the apparent simplicity of the process, the results were not very satisfactory. This was particularly true for the substrates **3c** and **3d** that afforded low yields of the target products **2c** and **2d**, together with relevant amounts of the 1,3-diol by-products **4c**,**d** (Table 2). A possible factor contributing to the low performance of the $NaBH_4$ reductions of **3c**,**d** is that these compounds have a very low population of the β-keto tautomers (**A**), and generally large amounts of β-enol ester (**B**) and hemiketal or *gem*-diol (**C**) forms, respectively (see Table 1). Even worse were the results obtained with **3a** in MeOH, where the hemiketal form **C** is largely predominant that resulted in a complex mixture of unidentified products.

Table 2. $NaBH_4$ reductions of **3a–f** in different solvents



3 2 4

R_F = (**a**) CF_3, (**b**) CHF_2, (**c**) C_2F_5, (**d**) $CClF_2$, (**e**) $CBrF_2$, (**f**) ClF_2

Product	Et_2O[a]	MeOH[a]	Toluene or C_6H_6[a]
2a	78 [2.5]	– [2.0][b]	94 [2.5]
2b	80 [1.5]	72 [0.5]	80 [2.0]
2c	29 [2.0][c]	<2 [1.5][d]	89 [3.5]
2d	44 [3.0][e]	40 [3.0][f]	92 [4.5]
2e	77 [1.5]	76 [1.5]	80 [4.5]
2f	72 [1.5]	71 [0.5]	73 [4.5]

[a] Yield (%) [reaction time (h)].
[b] Complex mixture.
[c] By-product **4c** was isolated in 29% yield.
[d] Complex mixture, containing low amounts (<5%) of **4c**.
[e] By-product **4d** was isolated in 30% yield.
[f] By-product **4d** was isolated in 20% yield.

To our surprise, the use of toluene or benzene (which provided identical results) as solvent proved to be extremely rewarding, affording the desired alcohols **2a–f** in high yields (Table 2), in spite of the poor solubility of $NaBH_4$ in these solvents. All of the substrates **3a–f** were reduced with very clean reactions, according to TLC and NMR analysis of the crude reaction mixtures, suggesting that nearly quantitative yields could be obtained simply by further prolonging the reaction times. An interpretation of these results in terms of tautomeric ratios of the substrates **3** in benzene is difficult (see Table 1), as the difference with respect to the other solvents is not dramatic. We believe that the improved performance should mainly depend on the reactivity of $NaBH_4$ in benzene or toluene, which is not commonly used for the reduction of carbonyl groups.[20]

The final transformation, step 3 (Scheme 2), was performed by heating β-hydroxy esters **2a–c** on P_2O_5,[5b] followed by standard or bulb to bulb distillation of the dehydration products **1a–c**, using a Kugelrohr apparatus. Compounds **1a–c** were obtained in good yields, in the range 65–75%, with very good purity, and nearly exclusive (*E*)-form.[21] However, attempts to obtain the chlorodifluoro derivative **1d** from **2d** according to the same procedure were unsuccessful, as the dehydration took place to a very small extent. Analogously, attempts to obtain the bromodifluoro and iododifluoro derivatives **1e**,**f** by dehydration of **2e**,**f** over P_2O_5 failed, producing extended decomposition. A number of other dehydration procedures were attempted for the transformation of **2d** into **1d**, including a variant of an optimized procedure recently reported for the dehydration of **2a** to **1a** (mesyl chloride, triethylamine),[22] H_2SO_4, H_2SO_4/AcOH, $SOCl_2$,[23] and DBU/$CHCl_3$,[8b] but the product **1d** was always obtained as a minor product in mixture with the carboxylic acids formed by hydrolysis of **2d** and **1d**, together with several other unidentified by-products. The reasons for the dramatic difference in reactivity of **2d–f** in comparison with **2a–c** are unclear. However, we suspect that the presence of halogens other than fluorine has an important role. This hypothesis is supported by the observation that, to our knowledge, none of the γ-halodifluoromethyl acrylates **1d–f** have been hitherto prepared by dehydration of the corresponding β-hydroxy esters **2d–f**.

In conclusion, we have carried out a detailed study on the feasibility of the preparation of β-fluoroalkyl acrylates **1a–f** in three steps from commercially available and inexpensive fluoroacetic esters. The procedure works very well for compounds **1a–c** containing only fluorine atoms, whereas the final dehydration step could not be performed successfully for the preparation of **1d–f**, which also contain chlorine, bromine, and iodine, respectively. In those cases, we recommend the use of an alternative methodology, described in the literature, relying on the Horner–Wadsworth–Emmons reaction of fluoroacetaldehydes with triethyl phosphonoacetate.[9] Finally, a detailed study on the tautomeric population of γ-fluoro-β-keto esters **3a–f** in different solvents has been performed.

3. Experimental

3.1. General details

Commercially available reagent-grade solvents were employed without purification. TLC was run on silica gel 60 F_{254} Merck. Flash chromatographies (FC) were performed with silica gel 60 (60–200 μm, Merck). ^1H, ^{13}C, and ^{19}F NMR spectra were run at 250, 400, or 500 MHz. Chemical shifts are expressed in parts per million (δ), using tetramethylsilane (TMS) as internal standard for ^1H and ^{13}C nuclei (δ_H and δ_C=0.00), while C_6F_6 was used as external standard (δ_F=−162.90) for ^{19}F. Compound **3a** was purchased from commercial sources.

3.2. Synthesis of β-keto esters 3b–f

3.2.1. Typical experimental procedure. To a solution of diisopropylamine (22.5 mL, 161 mmol) in dry THF (100 mL), a 2.5 M solution of *n*-butyl lithium in THF (64.4 mL, 161 mmol) was added at −40 °C, under nitrogen atmosphere. The temperature was allowed to increase slowly until 0 °C over 1 h, then the flask was cooled again to −78 °C and a solution of EtOAc (15.7 mL, 161 mmol) in THF (10 mL) was added dropwise. After 1 h a solution of ethyl difluoroacetate (8.47 mL, 80.5 mmol) in THF (8 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h, and after that time it was allowed to warm

to rt, then the reaction was quenched with saturated aqueous NH_4Cl, and extracted two times with EtOAc. The organic layer was washed with 1 M HCl, brine, dried over Na_2SO_4, and then the solvent was removed in vacuo affording **3b** (10.07 g, 80%) as a yellowish oil. The compound was used without further purification for the next step.

3.2.1.1. Ethyl 4,4-difluoro-3-oxobutanoate (3b). Physical, spectral, and analytical properties matched with those of the commercial compound obtained from Fluorochem Ltd (cat. Code 001566).

3.2.1.2. Ethyl 4,4,5,5,5-pentafluoro-3-oxopentanoate (3c). Physical, spectral, and analytical properties matched with those of the commercial compound obtained from Sigma–Aldrich.

3.2.1.3. Ethyl 4-chloro-4,4-difluoro-3-oxobutanoate (3d). Physical, spectral, and analytical properties matched with those described in the literature.[24]

3.2.1.4. Ethyl 4-bromo-4,4-difluoro-3-oxobutanoate (3e). Physical, spectral, and analytical properties matched with those described in the literature.[25]

3.2.1.5. Ethyl 4,4-difluoro-4-iodo-3-oxobutanoate (3f). Reddish oil. [Found: C, 24.78; H, 2.54. $C_6H_7F_2IO_3$ requires C, 24.68; H, 2.42%.] R_f=0.42 (Hex/EtOAc, 8:2); ν_{max} (film) 3446, 2986, 1739, 1373, 1098; ^{1}H NMR (400 MHz, $CDCl_3$). Keto form **A** δ: 1.27 (3H, t, J=7.2 Hz, *Me*), 3.77 (2H, s, CO*CH*$_2$), 4.18 (2H, q, J=7.2 Hz, O*CH*$_2$). Enol form **B**: 1.24 (3H, t, J=7.2 Hz, *Me*), 4.23 (2H, q, J=7.2 Hz, O*CH*$_2$), 4.61 (1H, br s, *OH*), 5.51 (1H, s,=*CH*). *gem*-Diol form **C**: 1.24 (3H, t, J=7.2 Hz, *Me*), 2.86 (2H, s, C(OH)$_2$*CH*$_2$), 4.61 (2H, br s, (*OH*)$_2$), 4.23 (2H, q, J=7.2 Hz, O*CH*$_2$). For all forms: ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.7, 13.8, 35.2, 40.1, 47.8, 49.8, 61.5, 61.6 (t, J=25.9 Hz), 61.8, 62.0, 87.3, 87.4 (t, J=312.1 Hz), 95.5 (t, J=326.3 Hz), 108.2, 164.5, 165.9 (t, J=25.5 Hz), 171.2, 185.3 (t, J=25.6 Hz); ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: form **A**: −62.4 (2F, s), form **B**: −55.8 (2F, s), form **C**: −57.9 (2F, s); m/z (EI) 314.9 [M+Na$^+$].

3.3. Reduction of β-keto esters 3a–f to β-hydroxy esters 2a–f

3.3.1. Typical experimental procedure. To a solution of **3d** (0.74 mmol) in toluene (5 mL) at 0 °C, $NaBH_4$ (0.78 mmol) was added portionwise and then the mixture was allowed to warm at rt. The slurry was stirred for 4.5 h at rt and then the reaction was quenched by careful addition of aqueous HCl (10%) at 0 °C. The phases were separated, and the aqueous phase was extracted twice with EtOAc, then the collected organic phases were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. Compound **2d** was obtained in very good purity, without further purification, in 92% yield. Spectral and analytical data of **2d** matched with those described in the literature.

3.3.1.1. Ethyl 4,4,4-trifluoro-3-hydroxybutanoate (2a). Physical, spectral, and analytical properties matched with those of the commercial compound obtained from Sigma–Aldrich.

3.3.1.2. Ethyl 4,4-difluoro-3-hydroxybutanoate (2b). Physical, spectral, and analytical properties matched with those described in the literature.[24]

3.3.1.3. Ethyl 4,4,5,5,5-pentafluoro-3-hydroxypentanoate (2c). Physical, spectral, and analytical properties matched with those described in the literature.[16]

3.3.1.4. Ethyl 4-chloro-4,4-difluoro-3-hydroxybutanoate (2d). Physical, spectral, and analytical properties matched with those described in the literature.[24]

3.3.1.5. Ethyl 4-bromo-4,4-difluoro-3-hydroxybutanoate (2e). Yellow oil. [Found: C, 29.26; H, 3.55. $C_6H_9BrF_2O_3$ requires C, 29.17; H, 3.67%.] R_f=0.41 (Hex/EtOAc 8:2); ν_{max} (film) 3447, 2987, 1723, 1106; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.2 Hz, *Me*), 2.68 (1H, dd, J=9.2 and 16.4 Hz, C*H*$_a$H$_b$CO), 2.79 (1H, dd, J=2.7 and 16.4 Hz, CH$_a$*H*$_b$CO), 3.9 (1H, s, *OH*), 4.21 (2H, q, J=7.2 Hz, O*CH*$_2$), 4.41 (1H, m, C*H*CF$_2$Br); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 36.0, 61.5, 73.1 (t, J=25.6 Hz), 123.6 (t, J=309.3 Hz), 170.5; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −58.7 (1F, dd, J_{FH}=10.1 Hz, J_{FF}=172.9 Hz), −61.1 (1F, dd, J_{FH}=10.1 Hz, J_{FF}=172.9 Hz); m/z (EI) 246.8 [M+H$^+$], 268.8 [M+Na$^+$], 284.9 [M+K$^+$].

3.3.1.6. Ethyl 4,4-difluoro-3-hydroxy-4-iodobutanoate (2f). Reddish oil. [Found: C, 24.63; H, 3.19. $C_6H_9F_2IO_3$ requires C, 24.51; H, 3.09%.] R_f=0.37 (Hex/EtOAc 8:2); ν_{max} (film) 3446, 2986, 1723, 1095; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.2 Hz, *Me*), 2.62 (1H, dd, J=9.2 and 16.4 Hz, C*H*$_a$H$_b$CO), 2.75 (1H, dd, J=2.4 and 16.4 Hz, CH$_a$*H*$_b$CO), 3.77 (1H, s, *OH*), 4.02 (1H, m, C*H*CF$_2$I), 4.21 (2H, q, J=7.2 Hz, O*CH*$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 36.5, 61.5, 74.6 (t, J=24.2 Hz), 109.2 (t, J=316.2 Hz), 170.2; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −50.8 (1F, dd, J_{FH}=10.1 Hz, J_{FF}=183.1 Hz), −55.1 (1F, dd, J_{FH}=10.1 Hz, J_{FF}=183.1 Hz); m/z (EI) 294.8 [M+H$^+$], 316.8 [M+Na$^+$].

3.4. Dehydration of β-hydroxy esters 2a–c to β-fluoroalkyl acrylates 1a–c

3.4.1. Typical experimental procedure. Alcohol **2a** (10.76 g, 57.8 mmol) was placed in a 50 mL flask and phosphorus pentoxide (4.1 g, 28.9 mmol) was added in one portion. The flask was shaken intermittently for 1 h (by hand). During this time a brown colored liquid was formed and heat was evolved. Distillation of the mixture yielded 6.68 g (39.7 mmol, 69% yield) of trifluorocrotonate **1a** (bp 113–117 °C) as colorless liquid.

3.4.1.1. Ethyl 4,4,4-trifluorobut-2-enoate (1a). Physical, spectral, and analytical properties matched with those of the commercial compound obtained from Sigma–Aldrich.

3.4.1.2. Ethyl 4,4-difluorobut-2-enoate (1b). Physical, spectral, and analytical properties matched those described in the literature.[8a]

3.4.1.3. Ethyl 4,4,5,5,5-pentafluoropent-2-enoate (1c). Physical, spectral, and analytical properties matched with those described in the literature.[8a]

Acknowledgements

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