Difluoromethylation Reactions of Ethyl Pyruvate with the TDAE – A Mild Approach to the Synthesis of 3,3-Difluoro-2-hydroxy-2-methyl-4-oxo-butyric Ethyl Esters Derivatives

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Abstract: New 3,3-difluoro-2-hydroxy-2-methyl-4-oxo-butyric ethyl esters derivatives are easily obtained in moderate to good yields from the tetrakis(dimethylamino)ethylene (TDAE) mediated reduction of a series of RCF_2X (X = Cl or Br) starting materials in the presence of ethyl pyruvate.

Key words: electron transfer, fluorine, tetrakis(dimethylamino)ethylene, ethyl pyruvate, nucleophilic additions

There continues to be an interest in the synthesis of fluorinated compounds because of the unique properties of such molecules.[1] For some years, we have been interested in the search of new methodologies to the synthesis of fluorine containing molecules;[2] among the recent studies developed in our laboratories, we have shown that the tetrakis(dimethylamino)ethylene (TDAE) reagent, a powerful electron-donor, was able to generate remarkably stabilized RCF_2 and CF_3 anions, in anhydrous DMF and other solvents.[3] Pawelke earlier demonstrated that the combination of CF_3I and TDAE could be used to prepare CF_3TMS from TMSCl.[4] A stepwise electron-transfer mechanism is presumed to take place. A series of electrophiles were found to react successfully with these anions, such as heteroaryl aldehydes and ketones, heteroaryl thiocyanates and acyl chlorides.

In a project devoted to the synthesis of new CF_2 containing molecules for biological evaluation, we sought to obtain a series of 3,3-difluoro-2-hydroxy-2-methyl-4-oxo-butyric ethyl esters derivatives by the reaction of halogeno-difluoromethylated substrates with TDAE in the presence of ethyl pyruvate.

3,3,3-Trifluoro-2-hydroxy-2-methyl propionic acid ethyl ester derivatives (and the corresponding Mosher's acid) have been prepared from the condensation of CF_3Br in the presence of the Zn in pyridine[5] or by the reaction of the Ruppert's reagent (CF_3TMS) with α-keto ester derivatives.[6] However to the best of our knowledge, related compounds with a difluoromethylene moiety are unknown.

Therefore a series of halogeno-difluoromethylated substrates **1**–**7** (Figure 1) chosen as good electron-acceptors (peak potentials measured at a glassy carbon electrode in anhydrous DMF are in the range of –1.15 to –1.65 V vs SCE), were engaged in coupling reactions with ethyl pyruvate, in the presence of TDAE, using anhydrous DMF as solvent (Scheme 1).

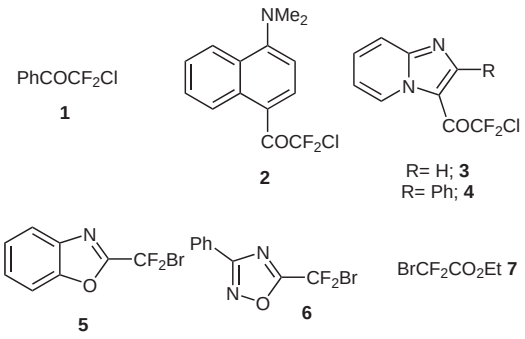
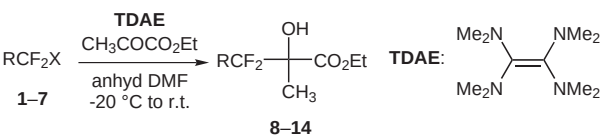


Figure 1



Scheme 1

In a typical experiment, 1.25 equivalents of TDAE (necessary for complete reaction of the starting ketone) was added dropwise to one equivalent of ketone **1** and three equivalents of ethyl pyruvate in anhydrous DMF at –20 °C, with the reaction being almost complete after two hours (TLC monitoring). After the usual work-up, a ^{19}F NMR spectrum of the crude product mixture revealed the presence of the desired alcohol **8**, which was characterized by an AB system (δ_F = –103.3 and –111.9 ppm/$CFCl_3$ with $J_{F\text{-}F}$ = 288 Hz). Two other fluorinated prod-

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ucts were also observed, the reduction product $PhCOCF_2H$ (δ_F = –125.7 ppm/$CFCl_3$; doublet with $^2J_{H\text{-}F}$ = 54.2 Hz) and a small amount of a product characterized by a singlet at δ_F = –63.1 ppm. Using $PhCF_3$ as internal standard, the yield of the desired alcohol adduct was estimated to be 72%, plus 18% of $PhCOCF_2H$. The alcohol adduct was isolated as a viscous, yellowish oil in 61% yield after purification by silica gel chromatography.[7] The other, minor product (a colourless viscous oil; 8%) was found to be $PhCOCF_2COCOCH_3$, which resulted from the nucleophilic attack of the difluoracetyl anion at the ester function. The other chlorodifluoracetylated ketones, **2**–**4**, were found to react in a similar fashion, with the alcohols adducts **9**–**11** being obtained in moderate to good yields (Scheme 2). In these cases, the two by-products detected by fluorine NMR of the crude reaction mixture were the $RCOCF_2COCOCH_3$ and $RCOCF_2H$ compounds.

The bromodifluoromethyl heterocycles **5**,**6** could also be used effectively in this coupling reaction. Fluorine NMR yields of alcohol adducts **12** and **13** were estimated to be 75% and 78% respectively and the reactions were usually complete in less than 2 hours. In contrast to the chlorodifluoroacetylated ketones substrates, none of the $RCF_2COCOCH_3$ by-products were obtained. The reaction with ethyl bromodifluoroacetate **7** was slower (completion after 8 hours), and the yield of desired alcohol **14** was rather low (25%), with the major product being HCF_2CO_2Et. This difference in reactivity may be attributed to the higher reduction potential of this substrate (peak potential was measured to be –1.65 V vs SCE at a glassy carbon electrode in anhydrous DMF). Increasing the amount of TDAE (from 1.25 to 2 equiv) resulted in almost quantitative yield formation of HCF_2CO_2Et.

Recent investigations have shown that the reaction can be also extended to methyl benzoyl formate $PhCOCO_2CH_3$ with similar yields being obtained (Figure 2).

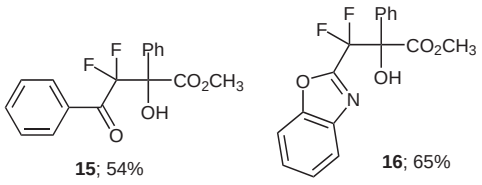
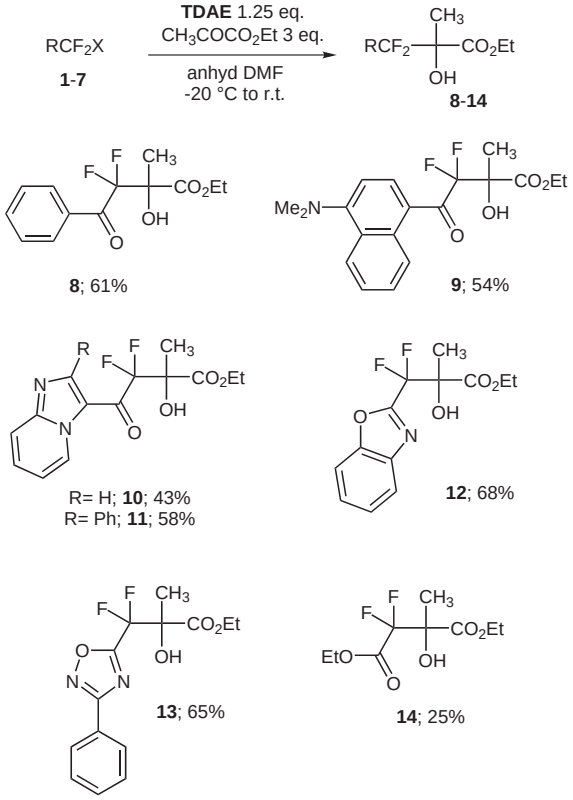
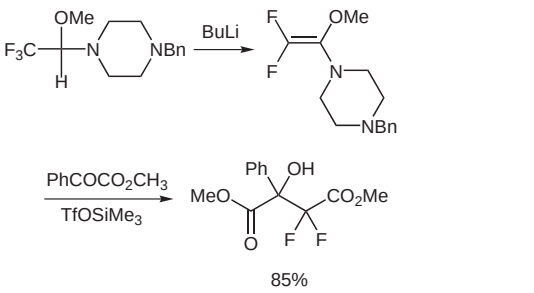


Figure 2

While our work was in progress, dehydrofluorination of a methylated hemiaminal of trifluoroacetaldehyde, and subsequent in-situ addition of the resulting ketene hemiaminal towards methyl benzoyl formate (and other electrophiles),[8] was found to be an alternative methodology to prepare similar derivatives (Scheme 3).



Scheme 2



Scheme 3

None of the yields have been optimised, and they should be able to be improved.

In conclusion, we have demonstrated, that under very mild conditions, new 3,3-difluoro-2-hydroxy-2-methyl-4-oxo-butyric ethyl ester derivatives could be obtained in reasonable yields using tetrakis(dimethylamino)ethylene (TDAE) as an efficient electron transfer reagent. The compounds synthesized in this work are potentially useful for biological applications. Further chemical elaboration of these derivatives is currently under investigation as well as enzymatic resolution of the racemates.

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(7) A typical procedure for the reaction between **1**, CH_3COCO_2Et and TDAE is as follows:
Into a three-necked flask equipped with a calcium chloride drying tube, and a nitrogen inlet was added, under nitrogen, 5 mL of anhyd DMF and then **1** (0.50 g, 2.62 mmol) followed by ethyl pyruvate (0.91 g, 7.9 mmol, 0.87 mL). The solution was cooled down to –20 °C, stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.63 g, 3.15 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at –20 °C for 1 h and then warmed up to r.t. for one hour (orange-red color). After this time TLC analysis [Hexane/EtOAc (60:40)] clearly showed that **1** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 30 mL of an aq NaCl solution. The aq solution was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic solutions washed with brine (3 × 30 mL), H_2O (3 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography [Hexane/EtOAc (60:40)] gave 0.43 g (1.58 mmol, 61%) of **8** as a yellowish viscous oil.
3,3-Difluoro-2-hydroxy-2-methyl-4-oxo-4-phenyl-butyric Acid Ethyl Ester: ^{1}H NMR ($CDCl_3$): δ = 1.31 (3 H, t, -*CH*$_3$CH$_2$), 1.66 (3 H, s, -CH$_3$), 4.32 (2 H, m, -CH$_2$), 7.4–7.7 (4 H, m), 8.10 (1 H, d, *J* = 7.2 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = –103.3 (1 F, d, *J* = 288 Hz), –119.2 (1 F, d, *J* = 288 Hz). GC/MS: M^+ = 272, $M^+ - CO_2Et$: 199, 156 ($PhCOCF_2$), 105 (PhCO), 77 (Ph). HRMS: Calcd for $C_{13}H_{14}F_2O_4$: 272.0860. Found: 272.0845.
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