Letter to the Editor

The 1-*N*-(methoxycarbonyl-2-phenylethyl)imino-2,2,2-trifluoroethanephosphonate systems are not stable enols of carboxylic esters

1. Introduction

In a recent paper in this journal it was suggested that 1-*N*-(1-methoxycarbonyl-2-phenylethyl)imino-2,2,2-trifluoroethanephosphonate systems **2**, R: Et, *n*-Pr, *i*-Pr, *n*-Bu, synthesized according to Eq. (1), tautomerize completely to their stable carboxylic acid ester tautomers **3** [1]. The evidence for the enol of ester structures was the ^{1}H NMR (CDCl$_3$) OMe signals at $\delta = 3.3$ ascribed to vinyl-OMe, the low field signal at $\delta = 8.3$ ascribed to the OH signal and the

$$CF_3COOH + PhCH_2\overset{CO_2Me}{\underset{}{C}HNH_2} \xrightarrow[Et_3N]{CCl_4, Ph_3P} PhCH_2\overset{CO_2Me}{\underset{}{C}HN=C(Cl)CF_3}$$
$$\mathbf{1}$$

$$\xrightarrow{P(OR)_3} PhCH_2\overset{CO_2Me}{\underset{PO(OR)_2}{C}HN=CCF_3} \rightleftharpoons PhCH_2\overset{C(OH)OMe}{\underset{PO(OR)_2}{C}N=CCF_3}$$
$$\mathbf{2} \qquad\qquad \mathbf{3}$$

$$(1)$$

lack of CH signals at $\delta = 5.0$ ppm, the IR signals at $3250\ cm^{-1}$ (OH) and the loss of optical purity of the products formed from L-(−)-phenylalanine methyl ester which may be due to racemization to the enols.

Stable enols of carboxylic acid esters are still uncommon and hence novel. Claims to their observations should be therefore checked critically. We had refuted earlier some claims for formation of several enols of carboxylic acid amides [2] and anhydrides [3] by using data for known species and computations of the energy of the carboxylic acid derivative and its enol, as well as by some experimentation. In this paper, we conclude that the alleged compounds **2/3** do not have the suggested enol structures.

2. Results and discussion

2.1. The synthetic method

The preparation of compound **1** followed the procedure of Tamura et al. [4] for the one-pot preparation of trifluoroacetimidoyl chlorides. Although **1** is apparently a new

compound, no data for it were given. The Arbuzov reaction of **1** gave **2**, which according to Eq. (1) occurs without structural rearrangement. The microanalysis data for compounds **2/3** fit any isomer of these compounds. The mass spectra which give either the molecular peak or fragments such as $m/z = 91$ ($C_7H_7^+$) or M-84 (M-CF$_3$-Me) were not applied for obtaining structural information. Only the NMR and IR data were used for structural assignment. A major discrepancy is shown by the ^{19}F NMR (CDCl$_3$, TFA) spectra which for all four systems reported signals at $\delta = 3.87$–4.01 (t, $J = 8.7$ Hz, CF$_3$). However, except in the unlikely possibility that a long range $^6J_{FH}$ coupling with the PhCH$_2$ protons, with no $^5J_{FH}$ coupling from the CH group is responsible for the CF$_3$ triplet, the CF$_3$ should be a doublet due to $^3J_{PF}$ coupling (neglecting ^1J coupling with the 1.1% ^{13}C). Consequently, the ^{19}F NMR data exclude the suggested structure for **3**.

However, the multiplicity of the signal and the J value are consistent with either the presence of a CF$_3$CH$_2$ moiety with a $^3J_{FH}$ if $^3J_{PF}$ is negligible or with a CF$_3$CH moiety with similar $^3J_{PF}$ and $^3J_{FH}$ values. How can a CF$_3$CH$_2$ or a CF$_3$CH moiety be created by the reaction in Eq. (1)? The paper of Tamura et al. [4] on which the reaction of PhCH$_2$CH(NH$_2$)CO$_2$Me was modeled showed that most compounds investigated gave the expected product with various amines. However, the reaction with benzylamine gave a rearranged product CF$_3$CH$_2$N=C(Cl)Ph, $J_{F,H} = 9.2$ Hz. This was ascribed to the initial formation of CF$_3$C(Cl)=NCH$_2$Ph, the analog of **1**, which underwent Cl-rearrangement involving S$_N$2′ reaction by Cl$^-$ and prototropy.

Application of a similar scheme for the reaction of PhCH$_2$CH(NH$_2$)CO$_2$Me will initially give **1** which will then rearrange according to Eq. (2) to give **4**, which could

$$\mathbf{1} \longrightarrow PhCH_2\overset{CO_2Me}{\underset{}{C}}=NCH(Cl)CF_3 \longrightarrow PhCH=\overset{CO_2Me}{\underset{}{C}}NHCH(Cl)CF_3$$
$$\mathbf{4} \qquad\qquad \mathbf{5}$$

$$PhCH(Cl)\overset{CO_2Me}{\underset{}{C}}=NCH_2CF_3 \longrightarrow PhC(Cl)=C\overset{CO_2Me}{\underset{NHCH_2CF_3}{}}$$
$$\mathbf{6} \qquad\qquad \mathbf{7}$$

$$(2)$$

further rearrange to **5**, **6** or **7** or to their mixture. Compounds **4** and **5** contain a CHCF$_3$ moiety and compounds **6** and **7** contain a CH$_2$CF$_3$ moiety. Reaction of **4**–**7** with P(OR)$_3$ will
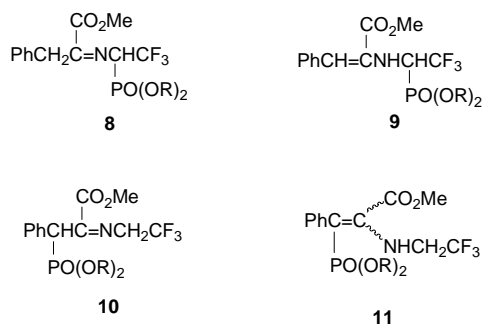
give products **8–11**, respectively, the isomers of **2** and **3** which contain a CF$_3$CH moiety. Compounds **8–11** can be also formed from **1** in the presence of P(OR)$_3$.

8 CO$_2$Me / PhCH$_2$C=NCHCF$_3$ / PO(OR)$_2$

9 CO$_2$Me / PhCH=CNHCHCF$_3$ / PO(OR)$_2$

10 CO$_2$Me / PhCHC=NCH$_2$CF$_3$ / PO(OR)$_2$

11 PhC=C / CO$_2$Me / NHCH$_2$CF$_3$ / PO(OR)$_2$

Regardless of the mechanism we believe that the compound reported by Ding and coworkers as **3** is probably one of compounds **8–11**. In none of them there is a CH(CO$_2$Me) moiety and an enol of the ester cannot be formed. The loss of $m/z = 84$ or of $m/z = 99$ fragments from "**2/3**", R: *n*-Bu, *i*-Pr, respectively, is consistent with the loss of CF$_3$CH$_3$ and CF$_3$CH$_2$NH$_2$ moieties, indicating the likely presence of a CF$_3$CHN moiety in the molecule.

2.2. Literature precedents

Several enols of carboxylic esters were suggested as reaction intermediates on the basis of kinetics [5], but no NMR data are available. Short-lived but observable enols, Ar$_2$C=C(OH)OR were observed [6] and for Ar: 2,4,6-*i*-Pr$_3$C$_6$H$_2$, R: Me, δ(OH) = 9.25 in CCl$_4$ [6b]. Other observable stable enols of esters gain stabilization from the presence of strong β-electron-withdrawing groups (EWGs) [7–9]. For five-substituted Meldrum's acid derivatives δ(OH) of the enol is in the range of 11.0–14.4 ppm [7]. For cyclopentadienes **12a–c** δ(OH) = 19.7−20.1 in Cl$_2$CDCDCl$_2$ [9].
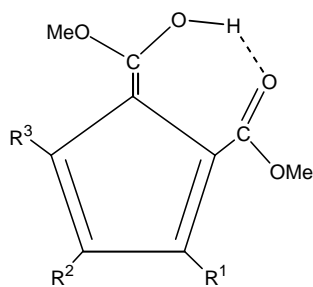
12a: R^1 = R^2 = R^3 = CO$_2$Me
  b: R^1 = R^2 = CO$_2$Me, R^3 = H
  c: R^2 = CO$_2$Me, R^1 = R^3 = H

13 CO$_2$Me / PhCH$_2$C=NCCF$_3$ / P(OH)(OR)$_2$
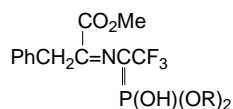
All these δ(OH) values are at a lower field than the alleged δ(OH) values for **2/3**. Moreover, the extreme lower field values are for systems with β-EWGs which are also hydrogen bond acceptors, such as the P=O of the N=C(CF$_3$)P(=O)(OR)$_2$

group in **3**. Structure **3** is therefore inconsistent with the suggested δ(OH) value of 8.3.

2.3. Computations

Computations [10] and experiment [11] show that for the parent system CH$_3$CO$_2$R/H$_2$C=C(OH)(OR), R: Me, Et, the equilibrium constant favors the ester over its enol by 19–22 orders of magnitude. A single EWG is insufficient to overcome this difference in related amide/enol systems [12], and alkyl groups increase very little the percentage of the enol form [2].

In order to investigate the relative stabilities of the two isomers, density functional B3LYP/6-31G** calculations [13] were conducted for isomers **2** and **3**, R: Me, as well as of another isomer, i.e. **13**, formed by tautomerization of the methine hydrogen to the phosphorus oxygen. For each isomer 5–8 different conformers were examined and confirmed to be local minima by frequency calculations. The relevant data are given in Table 1, and several selected conformations are given in Fig. 1. By comparing the most stable conformations of the three isomers we find that **3** and **13** are much less stable, by 12.6 and 12.8 kcal/mol than the ester form **2**. In terms of K_{Enol} (=[**3**]/[**2**] or [**13**]/[**2**]) the corresponding values are $10^{-9.2}$ and $10^{-9.4}$, respectively. The energy differences for the less stable conformers are mostly much larger, being up to 20 kcal/mol (Fig. 1).

2.4. Preliminary experiments

In order to compare the spectra of compounds **1** and **2**, the first step of Eq. (1) was conducted according to Tamura et al.'s method [4]. TLC of the reaction mixture showed that at least three compounds were formed. One of them was identified as compound **1** according to its ^{1}H, ^{13}C and ^{19}F NMR spectra and microanalysis: calcd. for C$_{12}$H$_{11}$ClF$_3$NO$_2$: C, 49.06; H, 3.75; N, 4.77; found: C, 49.53; H, 3.88; N, 4.66. Its highest mass spectral peak was at $m/z = 257$ which is consistent with [M − HCl]$^+$. A second compound with a nearly similar mass spectrum may be a geometrical (*E/Z*) isomer of **1**. A third compound had a completely different mass spectrum and was not investigated further.

Table 1
Calculated B3LYP/6-31G** free energy differences at 25 °C and K_{Enol} between ester **2** and its isomers, **3** and **13**

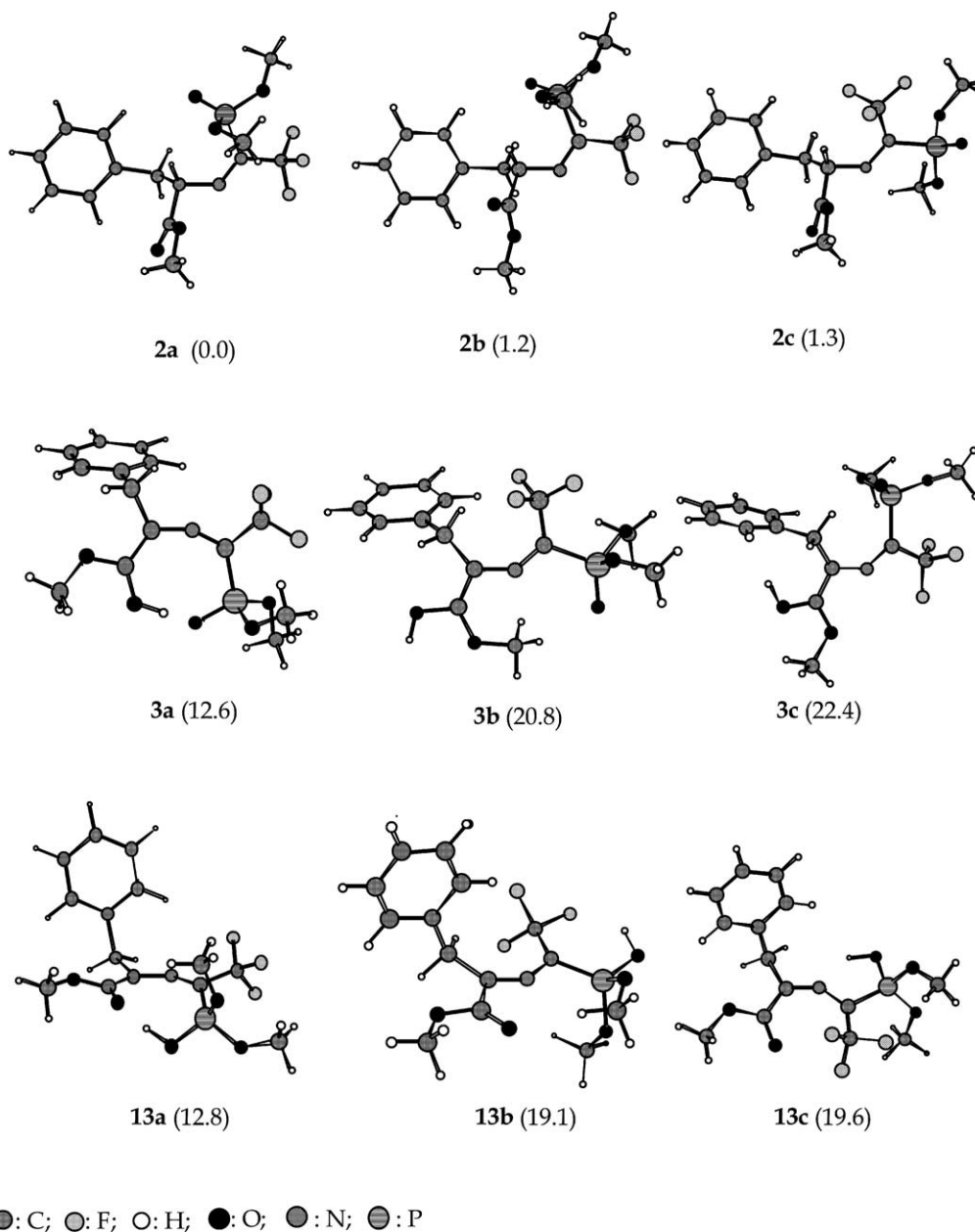| Compounds	ΔE (kcal/mol)	K_{Enol}
2a	0.0	
2b	1.2	
2c	1.3	
3a	12.6	$10^{-9.2}$
3b	20.8	
3c	22.4	
13a	12.8	$10^{-9.4}$
13b	19.1	
13c	19.6	

Fig. 1. Optimized structures of compounds **2**, **3**, and **13**. Numbers in parentheses are free energies at 25 °C relative to the most stable conformer of **2**. For each compound, three representative conformations are shown.

The CF$_3$ group of the three compounds appears as a singlet in the ^{19}F spectra.

Reaction of the "**1**" formed with P(OMe)$_3$ gave several products according to TLC. The major one was isolated and displayed the following spectra when impurities of <8% were neglected. The ^{1}H NMR spectra showed three 1H signals: a triplet of quartets (or overlapping quintets) centered at $\delta = 4.40$ ($J = 8$ Hz), a doublet of broad doublets centered at $\delta = 4.71$ with J of 4 and 12 Hz, and a singlet at $\delta = 6.84$. The MeO signals are a CO$_2$Me singlet at $\delta = 3.87$ and two OMe doublets $\delta = 3.80$ and 3.84, $^3J_{PH} = 11$ Hz and the 5H Ph is a multiplet. The signal at $\delta = 4.71$ disappeared after standing for 12 h with added D$_2$O at the expense of

formation of an HDO signal. In the ^{13}C NMR spectrum, the CF$_3$ centered at 124.1 is a quartet of doublets due to coupling with F and P ($^1J_{CF} = 282$ Hz, $^3J_{PC} = 8.6$ Hz), but in the ^{1}H coupled spectrum each doublet becomes an apparent triplet with $J = $ ca. 8 Hz. The singlet at $\delta = 117$, becomes a doublet of doublets, $^1J_{CH} = 160$ Hz ($J = 3.6$ Hz) in the CH coupled spectrum. The other aliphatic signals partly overlap so that assignments in the H coupled spectrum are unsafe. The uncoupled ^{19}F NMR spectrum (δ(CF$_3$Cl) = 0) shows a doublet at $\delta = -69.32$, $^3J_{PF} = 8$ Hz which becomes an apparent triplet in the hydrogen coupled spectrum.

The data indicate that the structure is not similar to that reported for **2** or interpreted as due to **3**. There is no low field

OH group, the CO_2Me group at $\delta = 3.87$ is at the position ascribed by the authors [1] to a normal ester group, rather than a vinylic OMe group and the CH groups are in different δ's than reported. The "CF_3 triplet" may be due to a coupling with both a P and a neighboring CH with similar J's. Structure **9** (Calcd. for $C_{14}H_{17}F_3NO_5P$: C, 45.78; H, 4.63; N, 3.81; found: C, 45.14; H, 4.66; N, 3.51) can account for the P=O couplings, for a CF_3CH moiety at $\delta = 4.40$, for the H–D exchange of the NH group a $\delta = 4.71$, for the prochirality of the OMe groups, for the δ of the CO_2Me group, for the $^1J_{CH}$ of 160 Hz for the =CH at $\delta = 6.84$ and for the loss of optical activity. The assumption of similar $^3J_{PF}$ and $^3J_{HF}$ values is reasonable but couplings to the phosphorous, which is known to give larger J's for couplings with further away carbons [14] complicate the spectrum and this structure is regarded as tentative only.

Since the compound itself is of no special interest neither to us nor to the authors [1] except for its claimed enol structure **3**, which was not formed, we do not plan a further experimental work.

3. Conclusion

We conclude that the enol of ester **3** is not formed and is much less stable than enol **2**. Moreover, the structure suggested for **2** is incompatible with the NMR spectra.

Acknowledgements

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