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Isomerisation reaction of a *gem*-bis-trifluoromethyl olefin in a basic medium: a kinetic study

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Abstract

The rearrangement of 5-phenyl-1,1,1-trifluoro-2-(trifluoromethyl)pent-2-ene to 5-phenyl-1,1,1-trifluoro-2-(trifluoromethyl)pent-3-ene has been studied by ^{19}F NMR in dimethylsulphoxide (DMSO). This isomerisation is catalysed by a base such as triethylamine. It is apparent that the olefin is more stable when the two trifluoromethyl groups are placed on a saturated carbon rather than on a vinylic carbon. In the isomerisation process, the part of triethylamine is to assist the intramolecular hydrogen transfer to give the more stable isomer.

Keywords: Isomerisation; Kinetic; ^{19}F NMR; Trifluoromethyl olefin

1. Introduction

The effects of perfluoroalkyl substitution at double bonds have remained relatively unexplored. Thermally, a single trifluoromethyl substituent slightly destabilises ethylene [1]. However, the influence of a second trifluoromethyl substituent is not known [2]. In the course of our studies on prenyl synthons [3] particularly on fluorinated analogues of isopentenyl adenines [4–6] we observed two different curious reactions: the anti-Michael addition of nucleophilic reagents on β,β-bis(trifluoromethyl)acrylic esters, followed by fluoride ion elimination and also the isomerisation of bis-trifluoromethyl olefins in a basic medium (Scheme 1).

In order to shed some light on the mechanism of this latter isomerisation reaction, we have performed a kinetic study.

2. Results

In order to check the eventual addition of mild nucleophiles to the double bond of a simple bis-trifluoromethyl alkene as previously observed with analogous substrates bearing another electron-withdrawing substituent (Scheme 1), we first examined the action of potassium thiophenoxide on olefin **1**. The phenyl group was only present in order to obtain high boiling points for the substrate and the products. Instead of the expected addition, we observed the isomerisation of **1** to **2** (*E* configuration) [7] in dimethylsulphoxide (DMSO) at room temperature (Scheme 2).

Inasmuch as the conjugation of the double bond with the aromatic ring in **2** may be a driving force for the isomerisation in this case, we also examined the behaviour of the homologous olefin **3**. Since its isomerisation to **4** (*E* configuration) also takes place in the presence of potassium thiophenoxide (91% yield) or triethylamine (quantitative) whose acidities are similar in DMSO ($pk_a = 9.0$ for Et_3NH^+ [8]; 9.8 for PhSH [9]), we must conclude that the above-mentioned conjugation is not the principal reason for the isomerisation (Scheme 3).

In order to trap a possible intermediate carbanion, the same experiments were repeated in the presence of good electrophiles such as benzaldehyde or diphenyldisulphide. These attempts were unsuccessful. So elucidation of the mechanism of this isomerisation needed kinetic investigations. For this purpose, ^{19}F NMR techniques appeared well adapted for monitoring the reaction [10]. Indeed, in both systems, the chemical shifts of the ^{19}F nuclei of the non equivalent trifluoromethyl groups of the starting material were deshielded in comparison with those for equivalent trifluoromethyl groups of **4**. Inasmuch as first kinetic experiments conducted in DMSO-d_6 were found to be insufficiently reproducible, probably because of the adventitious

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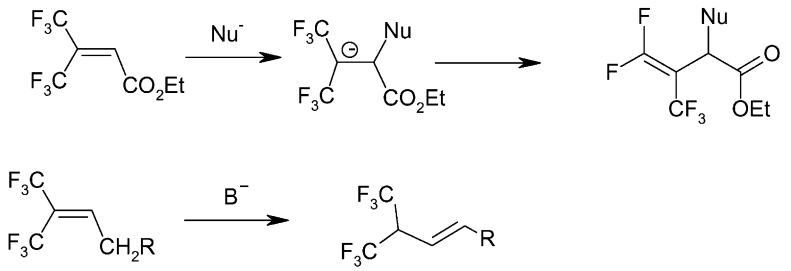
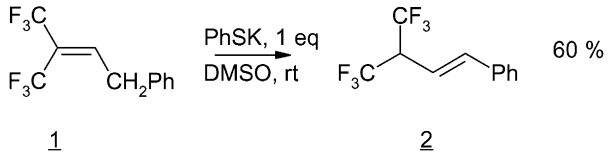
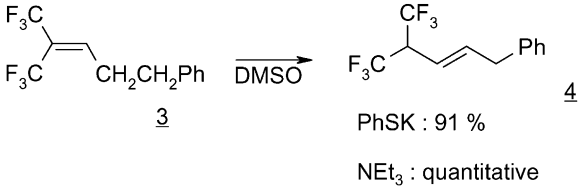


Scheme 1.



Scheme 2.



Scheme 3.

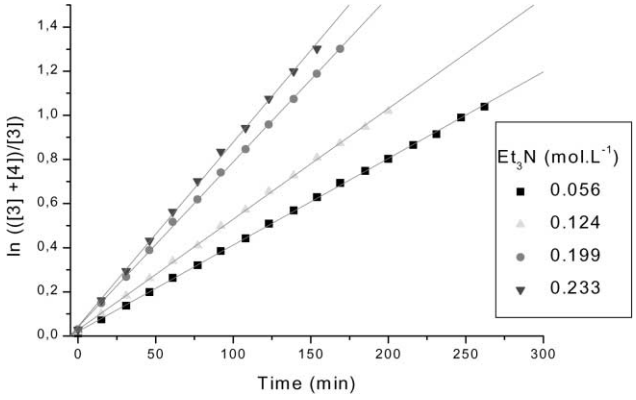


Fig. 1. First order substrate dependence of the plots $\ln\{([3]+[4])/[3]\}$ versus time.

water content of the solvent, we have preferred to run the kinetics in a DMSO-d_6/water mixture. We found that addition of 10 vol.% of water (i.e. 30% in mole fraction) allows clean and readily reproducible kinetics. During the accumulations of the free induction decays, we had to take care to not saturate the memories of the computers owing to the double height of the end product signal versus these of the substrate. It is also necessary to use a $\pi/6$ pulse width. Indeed, the three studied trifluoromethyl groups did not have identical relaxation times. We have measured $T1$ relaxation times for trifluoromethyl groups: 2.97 s for the left signal, 2.69 s for the right signal, 2.8 and 3.4 s in the cases of deuterated olefin (vide infra). For product **4**, the relaxation time was about 1 s. We used a delay of 0.5 s between two accumulations in order to obtain short time recorded spectra. In such a case, we had only a discrepancy of 2% between the integrations of the three signals. The time of running for a spectrum was 13 s.

Isomerisation of **3** to **4** by triethylamine in a DMSO-d_6/water (90/10) mixture was found to be first order substrate dependent, since the plots of $\ln\{([3]+[4])/[3]\}$ versus time were found to be linear with zero intercept (Fig. 1).

So for each experiment conducted at different triethylamine concentration the pseudo first order rate constant $k_{obs.}$ can be deduced from the slope of the plot (Table 1).

The excellent straight line obtained by plotting $k_{obs.}$ versus triethylamine concentration (Fig. 2) allowed the determination at 23°C of the first order rate constant ($k_s = 1.1 \times 10^{-3}\ min^{-1}$) for the catalytic solvent effect and the second order rate constant ($k_{Et_3N} = 4.9 \times 10^{-2}\ l\ min^{-1}\ mol^{-1}$) due to the base catalysis, according to the equation, $k_{obs.} = k_s + k_{Et_3N}\ [Et_3N]$.On performing an experiment in a DMSO-d_6/D_2O (90/10) mixture in the presence of triethylamine (0.329 mol l^{-1}, $k_{obs.} = 0.0163\ min^{-1}$) we only observed at 30 min few incorporation (≈5%) of deuterium in the final product, depicted by ^{19}F NMR by

Table 1
Triethylamine concentration and pseudo first order rate constant $k_{obs.}$ at 23°C

	Entry													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Et_3N (mol l^{-1})	0.033	0.056	0.063	0.088	0.124	0.139	0.177	0.190	0.199	0.214	0.227	0.233	0.240	0.308
$k_{obs.}$ ($\times 10^{-2}\ min^{-1}$)	0.23	0.39	0.42	0.53	0.74	0.76	1.03	1.11	1.11	0.17[a]	0.18[a]	1.23	1.29	1.56

[a] Reaction with **11**.

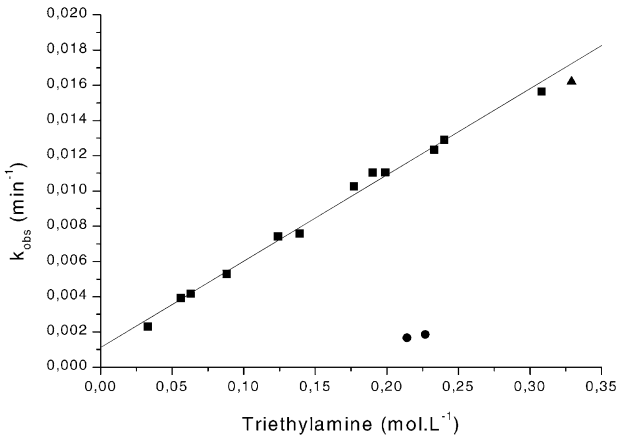
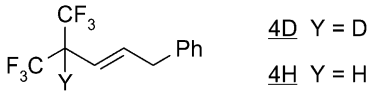


Fig. 2. Determination of rate constants (■) **3** to **4** in DMSO-d_6/H_2O (90/10), (●) **11** to **12** in DMSO-d_6/H_2O (90/10) and (▲) **3** to **4** in DMSO-d_6/D_2O (90/10).



4D Y = D

4H Y = H

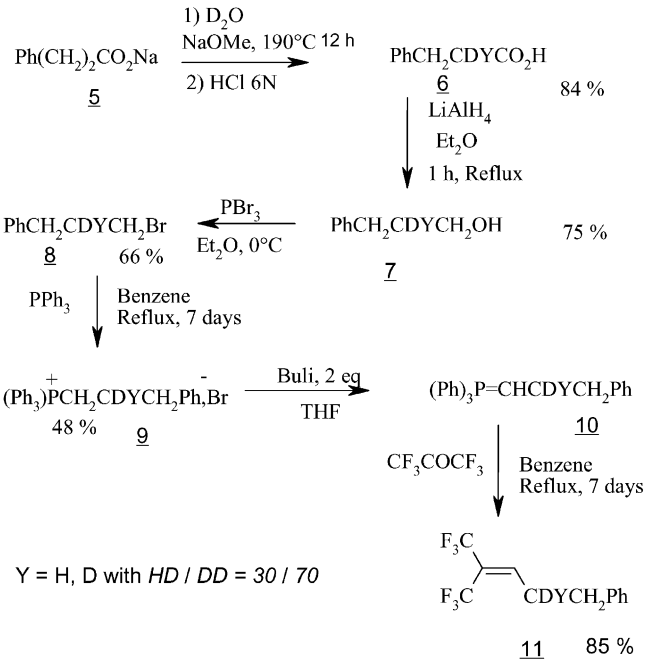
Scheme 4.

the large singlet of **4D** at –66.0 ppm, close to the doublet of **4** from 22 Hz upfield. So, the main part of this incorporation may be the result of an isotopic exchange of the tertiary allylic proton of **4H** (Scheme 4).

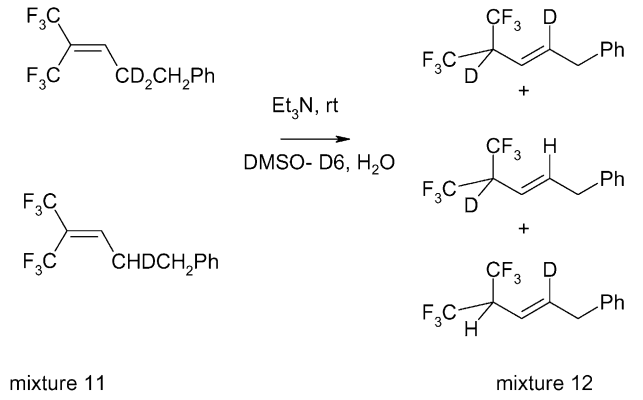
This important result shows that the tautomeric isomerisation of **3** to **4** is essentially an intramolecular process. In order to demonstrate such an assertion, we have prepared the analogue of **3**, deuterated in its allylic position, i.e. **11** in Scheme 5, and its isomerisation has been investigated.

Products **6**, **7** and **8** were already described [11]. Sodium phenylpropanoate **5** was heated at 190°C in deuterium oxide in the presence of sodium methylate; this reaction was repeated twice and the deuterated acid **6** was obtained with a 85% overall incorporation of deuterium (mono/bis: 0.3/0.7; this ratio was calculated from NMR spectral data). Then, this acid was reduced to alcohol **7** with lithium aluminum hydride and transformed to the corresponding bromide **8**. From its corresponding phosphonium salt **9**, a phosphorane **10** was prepared in order to react with hexafluoroacetone over 7 days in benzene at reflux. The deuterated olefin **11** was obtained as a mixture of dideuterated (**11DD**, 70%) and monodeuterated (**11HD**, 30%) species that give 85% of overall incorporation (Scheme 5). The kinetic of the isomerisation of this **11DD/11HD** mixture by triethylamine were monitored by ^{19}F NMR in the DMSO-d_6/water (90/10) mixture as described for **3**.

During these experiments, no change has been detected in the deuterium incorporation ratio of the product mixture **12** (Scheme 6) and an important isotopic effect $k_{H,Et_3N}/k_{D,Et_3N} = 6.1$ has been observed ($k_{D,Et_3N} = 8 \times 10^{-3}$ l min^{-1} mol^{-1}). Since this value corresponds to a 85% deuterium labelled compound, we could expect a larger isotopic effect, probably around 7 for the totally deuterated olefin **11DD**.



Scheme 5.



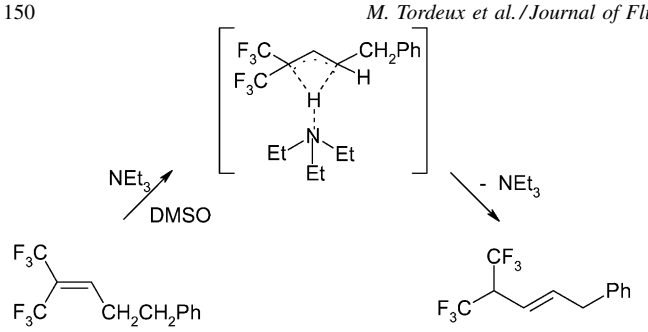
Scheme 6.

3. Discussion

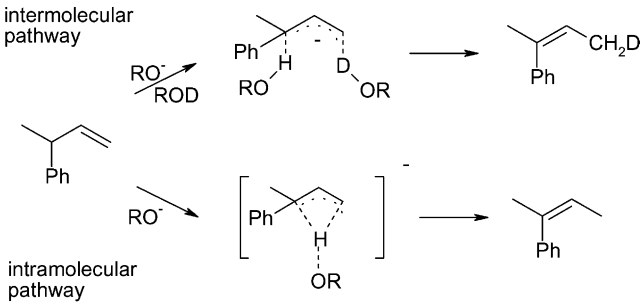
This important deuterium isotopic effect with the very small deuterium incorporation is observed when isomerisation of the proton olefin **3** by triethylamine was conducted in the DMSO-d_6/D_2O (90/10) mixture suggests an 1, 3–migration of the allylic hydrogen via an intermolecular pathway [12]. Such a mechanism is well described by a transition state in which the hydrogen is symmetrically centered between the triethylamine nitrogen and the carbons involved in the transfer (Scheme 7).

A similar proton transfer has been already reported by Cram in the base catalysed rearrangement of 3-phenylbut-1-ene by an alcoholate [13,14]. This rearrangement has been interpreted as a competition between intermolecular and intramolecular pathways (Scheme 8).

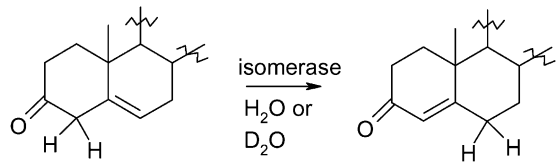
In our case, the intramolecular pathway is more important and may be compared to the base catalysed proton transfer



Scheme 7.



Scheme 8.



Scheme 9.

on 3-ketosteroids induced by an isomerase [15–17]. Indeed, in that system, 10% or less deuterium atoms were incorporated into the product from the medium and the isotopic effect was 4.1 (Scheme 9).

4. Conclusion

The rearrangement of the olefin **3** to its isomer **4** is slow in pure DMSO. This isomerisation is catalysed by a base such as triethylamine. A related rearrangement of a fluorinated prenyl halide has been observed previously [18]. It is apparent that the olefin is clearly more stable when the two trifluoromethyl groups are placed on a saturated carbon rather than on a vinylic carbon [1]. In the isomerisation process, the part of triethylamine is to assist the intramolecular hydrogen transfer to give a more stable isomer.

5. Experimental Section

(3-Phenyl-propyl)triphenylphosphonium bromide was provided from Lancaster, gaseous hexafluoroacetone and other compounds from Aldrich and deuterated DMSO from SDS.

NMR experiments: ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC 300 instrument. TMS was used as an internal standard. ^{13}C NMR spectra were obtained at 75.5 MHz. ^{19}F NMR spectra were recorded on the Bruker spectrometer at 282.4 MHz using $CFCl_3$ as reference. $CDCl_3$ was used as a solvent. *T*1 experiments were carried out using the Bruker program. The kinetic program was D1; ZE; GO = 3; WR#1; IF#1; D2; IN = 2; EXIT.

Delay before the first acquisition (D1), delay between to spectra (D2) (in seconds) and number of experiments (NE). For kinetic experiments, values for $\ln(a/(a-x))$ were calculated as: a = sums of signals areas at −59.0, −64.9 and −66.7 ppm; x = signal area at −66.7 ppm; the temperature was 23°C.

5.1. 4-Phenyl-2-(trifluoromethyl)-1,1,1-trifluorobut-2-ene *1*

1-Iodo-2-phenylethane (8 g, 0.034 mmol) and triphenylphosphine (10.5 g, 0.04 mmol) were refluxed in toluene (40 ml) for 24 h. The solvent was evacuated under vacuum and addition of tetrahydrofuran (THF) (50 ml) precipitated yellow crystals which were washed with THF to give (2-phenylethyl)triphenylphosphonium iodide (12.9 g, 0.026 mol, yield: 77%).

Then, butyllithium (10 mmol, 5 ml, 2 M in hexane) was added to a suspension of the phosphonium iodide (2.47 g, 5 mmol) in THF (50 ml) at −20°C. The deep red solution was stirred for 30 min at this temperature and an excess of gaseous hexafluoroacetone was introduced at −78°C. The mixture became pale yellow and was stirred for 3 h at this temperature and one night at room temperature. The reaction medium was poured into a 1/1 mixture of aqueous ammonium chloride/light petroleum. The organic phase was washed twice with water (50 ml) and dried over magnesium sulphate. Then the product was purified by column chromatography (silica gel 60 Å; dichloromethane as eluent) as an oil (0.6 g, 2.4 mmol, yield: 41%). ^{19}F NMR: −58.4 (CF_3 *cis*, q*q, $^{4}J_{FF}$ 7.1 Hz; J : 0.8 Hz), −64.9 (CF_3 *trans*, q*q, J: 1.5 Hz). ^{1}H NMR: 7.4 (5H, m) 6.89 (1H, t*m, J: 6.8 Hz) 3.78 (2H, d). CIMS (*m/z*) 254, 185, 165, 91, 77. Anal. calc. for $C_{11}H_8F_6$: C: 51.98, H: 3.17; Found: C: 52.32, H: 3.06%.

This product was not very stable. It could isomerise in DMSO solution to 1-phenyl-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene [7].

5.2. 1-Phenyl-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene *2*

Potassium thiophenoxide (0.11 g, 0.78 mmol) in dimethylsulphoxide (5 ml) was added to 4-phenyl-1,1,1-trifluoro-2-(trifluoromethyl)but-2-ene (0.2 g, 0.78 mmol) in DMSO (5 ml). The resulting mixture was stirred at room temperature for 1 h. Hydrochloric acid (3.5%, 10 ml) was added and the resulting mixture was extracted with diethylether (3 × 20 ml). The organic phases were washed with water,

dried over magnesium sulphate and evacuated under vacuum. 1-Phenyl-4,4,4-trifluoro-3-(trifluoromethyl)but-2-ene (0.12 g, 0.47 mmol, yield: 60%) was first purified by column chromatography (silica gel, 60 Å; eluents: pentane then pentane/dichloromethane, 7/3) then by preparative thin layer chromatography (silica gel, 60 Å, 1 mm; dichloromethane as eluent). ^{19}F NMR: −67.55 (d, J: 7.8 Hz). ^{1}H NMR: 7.4 (5H, m) 6.89 (1H, d, J: 16 Hz) 6.08 (1H, d*d, J: 16, 9.5 Hz) 4.68 (1H, m) CIMS (*m/z*) CI 254, 185, 165, 91, 77 (spectrum identical to that of 4-phenyl-1,1,1-trifluoro-2-(trifluoromethyl)but-2-ene).

5.3. 5-Phenyl-1,1,1-trifluoro-2-(trifluoromethyl)pent-2-ene **3**

Butyllithium (8.66 mmol, 5.41 ml, 1.6 M in hexane) was added to a suspension of (3-phenyl-propyl)triphenylphosphonium bromide (2 g, 4.43 mmol) in THF (25 ml) at −20°C. The deep red solution was stirred for 30 min at this temperature and an excess of gaseous hexafluoroacetone was introduced at −78°C. The mixture became pale yellow and was stirred for 3 h at this temperature and one night at room temperature. The reaction medium was poured into a 1/1 mixture of aqueous ammonium chloride/light petroleum. The organic phase was washed twice with water (50 ml) and dried over magnesium sulphate. Then the product was purified by column chromatography (silica gel, 60 Å; dichloromethane as eluent) as an oil (0.6 g, 2.23 mmol, yield: 51%). ^{19}F NMR: −59.0 (CF_3 *cis*, q*q, $^{4}J_{FF}$ 6.9 Hz; J :0.9 Hz) −64.9 (CF_3 *trans*, q*q, J : 1.5 Hz). ^{1}H NMR: 7.25 (5H, m) 6.76 (1H, t*m, J: 7.5 Hz) 2.8 (2H, m) 2.75 (2H, m). CIMS (*m/z*) 268, 177, 157, 91, 77. Anal. calc. for $C_{12}H_{10}F_6$: C: 53.74, H: 3.76; Found: C: 53.64, H: 3.52%.

This product was not stable in DMSO solution. It isomerises slowly to 1-phenyl-5,5,5-trifluoro-4-(trifluoromethyl)pent-2-ene.

5.4. 1-Phenyl-5,5,5-trifluoro-4-(trifluoromethyl)pent-2-ene **4**

Potassium thiophenoxide (0.16 g, 1.1 mmol) in dimethylsulphoxide (5 ml) was added to 5-phenyl-1,1,1-trifluoro-2-(trifluoromethyl)pent-2-ene 3 (0.3 g, 1.1 mmol) in DMSO (5 ml). The resulting mixture was stirred at room temperature for 1 h. Hydrochloric acid (3.5%, 10 ml) was added and the resulting mixture was extracted with diethylether (3 × 20 ml). Organic phases were washed with water, dried over magnesium sulphate and evacuated under vacuum. 1-Phenyl-5,5,5-trifluoro-4-(trifluoromethyl)pent-2-ene (0.27 g, 1.0 mmol, yield: 91%) was first purified by column chromatography (silica gel, 60 Å; eluents: pentane then pentane/dichloromethane, 7/3) then by preparative thin layer chromatography (silica gel, 60 Å, 1 mm; dichloromethane as eluent). ^{19}F NMR: −67.8 (d, J: 7.8 Hz). ^{1}H NMR: 7.2 (5H, m) 6.27 (1H, d*t, J: 15.1, 6.9 Hz) 5.48 (1H, d*d, J: 15.1, 9.5 Hz) 3.43 (2H, d, J: 6.9 Hz) 4.7 (1H, m) 4.68 (1H, m) CIMS (*m/z*) 254, 185, 165, 91, 77 (spectrum identical to 5-phenyl-1,1,1-trifluoro-2-(trifluoromethyl)pent-2-ene, **3**).

5.5. 2,2-Dideuterio-3-phenylpropanoic acid **6**

Sodium 3-phenylpropanoate **5** was prepared by reaction of 3-phenylpropanoic acid and sodium hydride in ether. The salt (10.9 g, 0.063 mol), sodium methylate (3.42 g, 0.063 mol) and 10 ml of deuterium oxide were heated at 200°C in a 50 ml autoclave for 24 h. Then, 6 N hydrochloric acid (100 ml) was added and the organic acid was extracted with ether (4 × 100 ml). The organic layer was dried over magnesium sulphate. The reaction was repeated. After evacuation of the solvent under vacuum, the **HD/DD** ratio of 2,2-dideuterio-3-phenyl-propanoic acid was calculated from the NMR spectrum by integration of ^{1}H NMR signals 2.42 (0.3H) versus 2.72 ppm (2H). The aromatic ring signal at 7.16 ppm (5H) was also used as reference.

GC–MS (*m/z*): 151 (16.8), 152 (36.7), 153 (9.4), 107 (44.7), 106 (100), 105 (37.5).

5.6. 2,2-Dideuterio-3-phenylpropan-1-ol **7**

Crude acid **6** and lithium aluminum hydride (4.3 g, 0.11 mol) in ether (300 ml) were refluxed for 1 h. Water (5.2 ml), sodium hydroxide (15%, 5.2 ml) then water (5.2 ml) was added; the solid was filtered. The organic layer was washed with brine and dried over magnesium sulphate. The reduction was repeated twice. After evacuation under vacuum, the crude alcohol (6.2 g) was obtained in a 75% yield.

^{1}H NMR: (with integration) 7.20 (5H), 3.59 (2H), 2.74 (2H), 1.84 (0.3H).

GC–MS (*m/z*): 139 (1.1%), 138 (4.7%), 137 (2%), 120 (100%), 119 (90.5%), 107 (16.6%), 91 (44.4%).

5.7. 1-Bromo-2,2-dideuterio-3-phenylpropane **8**

To the alcohol **7** (5.7 g) in ether (33 ml) was added phosphorus tribromide (4 ml) and the mixture was stirred for 24 h, poured on ice, then extracted with ether (3 × 30 ml). The organic layer was washed with saturated sodium hydrogencarbonate (50 ml), with brine (2 × 50 ml) and dried over magnesium sulphate. After evacuation of the solvent under vacuum, the product **8** was isolated in a 77% yield by column chromatography (silica gel, eluents: chloroform, then chloroform/ethyl acetate 80/20).

^{1}H NMR: (with integration) 7.20 (5H), 3.35 (2H), 2.75 (2H), 2.15 (0.3H).

GC–MS (*m/z*): 201 (25.1%), 200 (19.8%), 199 (33.8%), 198 (18.3%), 91 (100%).

5.8. 2,2-Dideuterio-3-phenylpropyl)triphenyl phosphonium bromide **9**

Bromide **8** (2 g, 0.01 mol), triphenylphosphine, (3 g, 0.011 mol) and a small quantity of sodium iodide were

refluxed in benzene (30 ml) for 7 days. An oily product was obtained which was precipitated in THF (20 ml). Crystals (2.2 g, 4.8 mmol, yield: 48%) were filtered and washed with benzene and pentane. ^{1}H NMR: (with integration) 7.78 (15H), 7.25 (5H), 3.85 (2H), 3.0 (2H).

*5.9. 2,2-Dideuterio-1,1,1-trifluoro-2-trifluoromethylpent-2-ene **11***

Its preparation from the phosphonium bromide **9** (3 g, 6.5 mmol) was similar to that of **3**. Compound **11** was obtained in 85% yield (1.47 g, 5.5 mmol).

^{19}F NMR: −59.0 (3F, d J : 0.9 Hz), −64.9 (3F, d J : 1.5).

^{1}H NMR: (with integration) 7.25 (5H), 6.74 (1H), 3.75 (0.3H), 2.75(2H).

*5.10. 2,2-Dideuterio-1,1,1-trifluoro-2-trifluoro-methylpent-3-ene **12***

From kinetic experiments. In the mixture DMSO-d_6/H_2O: ^{19}F NMR: −66.0 (s), −65.95 (d).^{1}H NMR: 7.21 (5H), 5.43 (1H), 4.72 (0.15H), 3.42 (2H).

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