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Research Article

The synthesis and characterization of 2-Trideuteriomethyl and 2,2-Di(trideuteriomethyl) Aryl Ketones

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Summary

Results are reported on the synthesis and characterization of a variety of trideuteriomethyl aryl ketones. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: deuterium; enolates; ^{13}C NMR spectroscopy; 2-methyl aryl ketones; trideuteriomethyl substitution

Introduction

The selective incorporation of non-radioactive isotopic labels into organic molecules for biological and chemical studies is an increasingly important area.[1] For example, the use of a trideuteriomethyl (CD_3) group within synthesis is widespread; it has found application in the elucidation of reaction mechanisms[2] and the determination of ambiguous stereochemistry.[3,4] The majority of these studies have relied on this CD_3 substituent being spectroscopically inactive (through the use of ^1H NMR spectroscopy).[5] By comparison, studies involving

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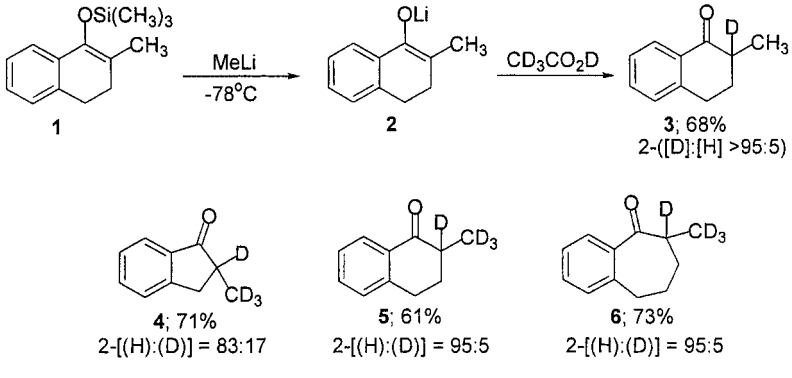
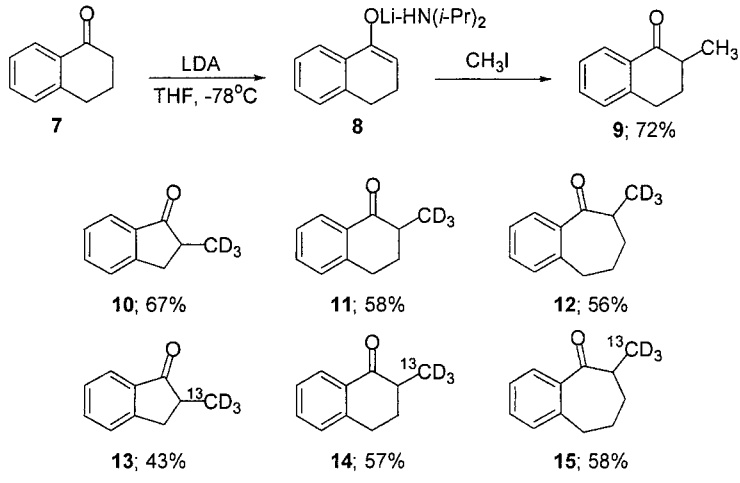
^{13}C NMR spectroscopy are rare.[6] This is not that surprising due to the long[7] (T_1) relaxation time for a CD_3 substituent which causes the signal intensity of the required septet (1:3:6:7:6:3:1) to be particularly weak. The intensity of this signal in the ^{13}C NMR spectra can be improved by running the sample neat or as a concentrated solution in the presence of a suitable solvent. However, this strategy does rely on the sample being readily available and in reasonable quantity (>1 g). Usually, this procedure is only practical for samples which do not contain hydrogen such as common NMR solvents (e.g. acetone-d_6, DMSO-d_6 and methanol-d_4).

We have recently been interested in the regioselective deuteriation of 'base-free' enolates such as **2** (formed by the addition of MeLi to the silyl enol ether **1**) to give 2-deuterio-2-methyl aromatic ketones **3** under kinetic control. We have extended this methodology further towards the synthesis of perdeuteriated ketones like **4**, **5** and **6**.[8] During the course of this study we became interested in the synthesis and characteristic behaviour of related trideuteriomethyl (CD_3) groups using ^{13}C NMR spectroscopy Scheme 1.

We now report the synthesis of a variety of CD_3 and $^{13}CD_3$ containing aryl ketones, and comment on the relative shape and intensity of the associated signal by ^{13}C NMR spectroscopy. We originally chose an aryl ketone framework for our study since many of the required non-labelled methyl derivatives, such as 2-methyltetralone **9** have been previously[1] synthesized in our laboratory by the simple addition of methyl iodide to the lithium enolate **8** – formed by the addition of lithium diisopropylamide (LDA) to the parent ketone, tetralone **7**. We argued that replacing methyl iodide for an isotopic



Scheme 1. Synthesis of 2-deuterio aryl ketones 3–6



Ketone	13	14	15
δ_C C(2)	41.8 ppm, *d* $^1J_{C,C}$ = 35.1 Hz	42.4 ppm, *d* $^1J_{C,C}$ = 36.1 Hz	44.0 ppm, *d* $^1J_{C,C}$ = 36.1 Hz
δ_C $^{13}CD_3$	15.6 ppm, *septet* $^1J_{C,D}$ = 19.6 Hz	14.6 ppm, *septet* $^1J_{C,D}$ = 19.4 Hz	15.6 ppm, *septet* $^1J_{C,D}$ = 19.6 Hz

Scheme 2. Synthesis of 2-trideuteriomethyl aromatic ketones 10–15

variant, like trideuteriomethyl iodide (CD_3I), should allow access to the required trideuteriomethyl derivatives. By treatment of tetralone **7**, indanone **16** and benzosuberone **19** with an appropriate amount of LDA and trideuteriomethyl iodide gave the corresponding 2-trideuteriomethyl **10–12** and 2,2-di-trideuteriomethyl derivatives **20**, **23** and **27** in good chemical yield Scheme 2.

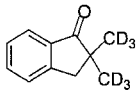
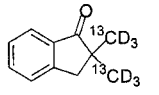
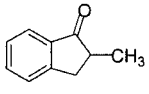
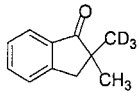
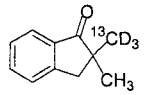
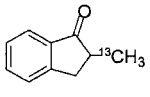
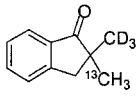
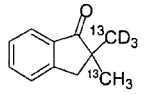
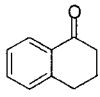
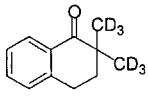
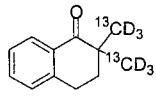
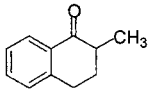
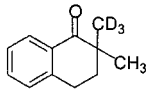
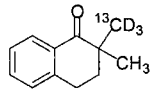
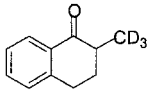
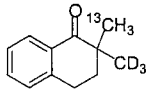
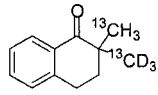
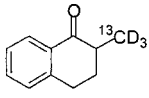
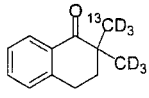
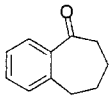
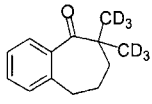
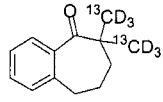
These derivatives were easily characterized using ^{1}H NMR spectroscopy; the most noticeable feature was the disappearance of one or both of the two C(2)H_2 protons adjacent to the carbonyl group. Equally, the required septet (1:3:6:7:6:3:1) for the CD_3 substituent was generally missing from the ^{13}C NMR spectra. However, for the 2-trideuteriomethyl aryl ketone **10**, the CD_3 group gave a triplet-like signal (ratio 6:7:6 – $^1J_{C,H}$ = 19.8 Hz) at 15.5 ppm (in the ^{13}C NMR spectrum), indicating only three (6:7:6) of a possible seven lines of the septet (1:3:6:7:6:3:1), whereas for those derivatives **20**, **23** and **27** which contain two magnetically equivalent trideuteriomethyl groups, the signal intensity was improved slightly to reveal a quintet (ratio 3:6:7:6:3) at

approximately 24 ppm in the ^{13}C NMR spectra with characteristic C,D coupling of 20 Hz. This lack of signal intensity was due to a longer (T_1) relaxation time associated with this CD_3 substituent because of the small magnetic moment associated with the neighbouring deuterium atom. For example, the relaxation time for a $^{13}CD_3$ substituent in 2,2-di-trideuteriomethyl-[^{13}C]-indanone **28** was found to be; $T_1 = 28.21$ seconds and $T_2 = 0.76$ seconds (determined by ^{13}C NMR spectroscopy at 150 MHz in $CDCl_3$).

The full seven lines of the septet could only be observed by incorporation of a C-13 isotopic label on the carbon bearing the CD_3 group. The required 2-trideuteriomethyl-[^{13}C] and 2,2-trideuteriomethyl-[^{13}C]-labelled ketones **13–15**, and **28**, **31** and **34**, respectively, were easily synthesized in good yield using our standard deprotonation-methylation protocol by replacing CD_3I with $^{13}CD_3I$. The presence of this C-13 label allowed the carbon–deuterium coupling to be accurately determined (Table 1: $^1J_{C,D} = 19.4 \pm 0.2$ Hz). We have also assumed that similar C–D couplings (in the natural abundance ^{13}C NMR spectra) are also present in the non-^{13}C labelled ketones (e.g. 2-trideuteriomethyl tetralone **11**) even though the original septet for the CD_3 group in the ^{13}C NMR spectrum was absent.

We additionally synthesized a series of unsymmetrically labelled 2,2-dimethyl aryl ketones **21**, **22**, **24–26**, **29**, **30**, **32** and **33** to probe the effect of having different isotopically labelled methyl substitutents present in the same molecule. These were efficiently synthesized by deprotonation of the corresponding mono-substituted aryl ketone **9**, **11**, **14**, **17** and **18** with LDA and methylation using an appropriately isotopically labelled methyl iodide. For those ketones **21**, **22**, **24**, **25** and **26** which contained a single CD_3 group, no carbon signal for the CD_3 substituent was observed by ^{13}C NMR spectroscopy, whereas for those derivatives **26** and **28–34** which contained two ^{13}C groups, the required septet (1:3:6:7:6:3:1) was easily detected in the ^{13}C NMR spectra (between 23.6 and 24.5 ppm), slightly downfield with respect to the 2-methyl aryl ketones. There was also found to be only slight variation in carbon–deuterium coupling (19.2–20.2 Hz: Table 1). This difference was presumably due to the combination of different isotopic substitution patterns being present. Furthermore, there was also found to be a negative isotope shift for a $^{13}CD_3$ substituent with respect to both a CH_3 group (0.19 ppm – from **32**) and a $^{13}CH_3$ group (0.57 ppm – from **33**). This chemical shift difference was due to a combination of the more

Table 1 Synthesis of CD_3 and $^{13}CD_3$ labelled aryl ketones 20–34

Entry	Starting material Ketone	Products CD_3 labelled ketone[a]	Products $^{13}CD_3$ labelled ketone[b]	δ_C C(2)	δ_C $^{13}CD_3$
1	 **16**	 **20**; 67%	 **28**; 41%	45.0 ppm, *t* $^1J_{C,C}$ = 33.8 Hz	24.4 ppm, *septet* $^1J_{C,D}$ = 19.6 Hz
2	 **17**	 **21**; 74%	 **29**; 67%	45.3 ppm, *d* $^1J_{C,C}$ = 35.1 Hz	24.5 ppm, *septet* $^1J_{C,D}$ = 19.6 Hz
3	 **18**	 **22**; 72%	 **30**; 65%	45.5 ppm, *t* $^1J_{C,C}$ = 35.5 Hz	24.5 ppm, *septet* $^1J_{C,D}$ = 19.6 Hz
4	 **7**	 **23**; 78%	 **31**; 71%	41.1 ppm, *t* $^1J_{C,C}$ = 33.7 Hz	23.7, *septet* $^1J_{C,D}$ = 19.6 Hz
5	 **9**	 **24**; 61%	 **32**; 73%	41.2 ppm, *d* $^1J_{C,C}$ = 35.0 Hz	23.7, *septet* $^1J_{C,D}$ = 20.0 Hz
6	 **11**	 **25**; 72%	 **33**; 73%	41.4 ppm, *t* $^1J_{C,C}$ = 35.6 Hz	23.6, *septet* $^1J_{C,D}$ = 19.2 Hz
7	 **14**	 **26**; 76%	—	41.2 ppm, *d* $^1J_{C,C}$ = 34.6 Hz	23.6, *septet* $^1J_{C,D}$ = 20.2 Hz
8	 **19**	 **27**; 68%	 **34**; 44%	44.0 ppm, *t* $^1J_{C,C}$ = 34.5 Hz	24.6, *septet* $^1J_{C,D}$ = 19.2 Hz

[a] Synthesized by the addition of LDA, followed by CD_3I.
[b] Synthesized by the addition of LDA, followed by $^{13}CD_3I$.

electropositive deuterium atom and C-13 labelled carbon atom causing the isotopically labelled methyl substituent to resonate at a slightly higher field.

In conclusion, we have reported an efficient synthesis of a variety of 2-deuteriomethyl aryl ketones **10**–**15** and **20**–**34**. We have shown that the signal intensity and observed splitting pattern associated with a CD_3 substituent (by ^{13}C NMR spectroscopy) is varied. The required septet (1:3:6:7:6:3:1) could only be detected by using a C-13 label to increase the signal intensity of the trideuteriomethyl (CD_3) signal. The effect of deuterium in a CD_3 group lowers the intensity at least 20 times (with respect to a CH_3 group) giving rise to a septet (1:3:6:7:6:3:1) with a characteristic ($^1J_{C,D}$) ^{13}C–D coupling of approximately 20 Hz. Furthermore, we have also noticed the relative signal intensity in the ^{13}C NMR spectra for each isotopic methyl substituent is in the order; $^{13}CH_3 > {}^{13}CD_3 > CH_3 > CD_3$. The additional presence of a ^{13}C label is particularly interesting for both $^{13}CH_3$ and $^{13}CD_3$ containing derivatives, since this gives rise to either a doublet ($^1J_{C,C} = 35$ Hz) or triplet ($^1J_{C,C} = 35$ Hz) in the ^{13}C NMR spectra for the C(2) position when either one or two C-13 labelled methyl substituents ($^{13}CH_3$ and/or $^{13}CD_3$) are present.

Typical procedure: 2-trideuteriomethyltetralone **11**-d_3-tetralone **7** (0.70 g, 0.63 ml, 6.8 mmol) was slowly added to a solution of LDA (4.5 ml, 1.5 M in THF, 6.8 mmol) in THF (20 ml) at −78°C and stirred for 30 min. Trideuteriomethyl iodide-d_3 (0.98 g, 0.4 ml. 6.8 mmol) was added dropwise and the resulting solution was allowed to warm to room temperature, and stirred for 12 h. The reaction was quenched by the addition of water (10 ml). A solution of NH_4Cl (saturated, 10 ml) was added and the mixture was extracted with ether (3×50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum (b.p. 40–60°C)-ether (19:1) to give 2-trideuteriomethyltetralone **11**-d_3 (0.64 g, 58%) as an oil; R_f [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm 2061 (CD), 1681 (CO); δ_H(250 MHz, $CDCl_3$) 8.05 (1 H, d, *J* 7.7, CH; Ar), 7.45 (1 H, t, *J* 7.7, CH; Ar), 7.31 (1 H, d, *J* 7.7, CH; Ar), 7.22 (1 H, d, *J* 7.7, CH; Ar), 3.10–2.93 (2 H, m, CH_2), 2.62–2.54 (1 H, dd, *J* 11.9 and 4.4, MeCH), 2.25–2.15 (1 H, m, CH_ACH_B) and 1.96–1.80 (1 H, m, CH_ACH_B); δ_c(100.6 MHz, $CDCl_3$) 200.7, 144.2, 133.0, 132.4, 128.7, 127.4, 126.5, 42.4, 31.3 and 28.8 (Found M^+, 163.1083. $C_{11}H_9D_3O$ requires M, 163.1076); *m*/*z* 164 (100%, M + H) and 163 (60, M). The absence of the septet [1:3:6:7:6:3:1] around 15 ppm for the CD_3 substituent in the ^{13}C NMR spectra is common due to a long relaxation time.

2-Trideuteriomethyl-[^{13}C]-tetralone **14**-d_3: In the same way as 2-trideuteriomethyl tetralone **11**-d_3, tetralone **7** (1.4 g, 1.27 ml, 9.8 mmol), LDA (6.5 ml, 1.5 M in THF, 9.8 mmol) and methyl-[^{13}C]-iodide-d_3 (1.4 g, 0.6 ml. 9.8 mmol) gave, after column chromatography on silica get eluting with light petroleum ether–ether (19:1) 2-trideuteriomethyl-[^{13}C]-tetralone **14**-d_3 (0.91g, 57%) as an oil; R_f [light petroleum (40–60°C):ether (9:1)] 0.5; ν_{max} (film)/cm 2065 (CD) and 1685 (CO); δ_H(250 MHz, $CDCl_3$) 8.05 (1 H, d, *J* 7.7, CH; Ar), 7.45 (1 H, t, *J* 7.7, CH; Ar), 7.32 (1 H, d, *J* 7.5, CH; Ar), 7.24 (1 H, d, *J* 7.5, CH; Ar), 3.12–2.93 (2 H, m, CH_2), 2.62–2.53 (1 H, m, MeCH), 2.26–2.14 (1 H, m, CH_ACH_B) and 1.97–1.79 (1 H, m, CH_ACH_B); δ_c (67.5 MHz, $CDCl_3$) 200.7, 144.1, 133.1, 132.7, 128.7, 127.4, 126.6, 42.4 (1 C, d, $^1J_{C,C}$ 36.1, C^{13}C), 31.3, 28.8 and 14.6 (1 C, septet [1:3:6:7:6:3:1], $^1J_{C-D}$ 19.4, $^{13}CD_3$) (Found M^+, 164.1133. C_{10} $^{13}CH_9D_3O$ requires M, 164.1102).

2,2-Di(trideuteriomethyl)tetralone **23**-d_6: In the same way as 2-trideuteriomethyl tetralone **11**-d_3, tetralone **7** (0.81 g, 0.73 ml, 5.5 mmol), LDA (4.5 ml, 1.5 M in THF, 11 mmol) and methyl iodide-d_3 (1.61 g, 0.7 ml. 11 mmol) gave, after column chromatography on silica get eluting with light petroleum ether–ether (19:1) the 2,2-di(trideuteriomethyl)tetralone **23**-d_6 (0.77 g, 78%) as an oil; R_f [light petroleum (40-60°C):ether (9:1)] 0.6; ν_{max} (film)/cm 2062 (CD) and 1679 (CO); δ_H (250 MHz, $CDCl_3$) 8.05 (1 H, d, *J* 7.5 CH; Ar), 7.42 (1 H, t, *J* 7.5, CH; Ar), 7.25 (1 H, t, *J* 7.5, CH; Ar), 7.20 (1 H, d, *J* 7.5, CH; Ar), 2.95 (2 H, t, *J* 6.3, CH_2) and 1.95 (2 H, t, *J* 6.3, CH_2); δ_c(62.5 MHz, $CDCl_3$) 202.9, 143.4, 132.9, 131.5, 128.7, 127.9, 126.6, 41.2, 36.5 25.7 and 23.4 (2 C, quintet [3:6:7:6:3], $^1J_{C-D}$ 20.5, CD_3) (Found MH^+, 181.1508. $C_{12}H_9D_6O$ requires MH, 181.1500).

2,2-Di(trideuteriomethyl)-[^{13}C]-tetralone **31**-d_6: In the same way as 2-trideuteriomethyl tetralone **11**-d_3, tetralone **7** (0.2 g, 0.18 ml, 1.37 mmol), LDA (1.8 ml, 1.5 M in THF, 2.74 mmol) and trideuteriomethyl-[^{13}C] iodide-d_3 (0.4 g, 0.18 ml. 2.74 mmol) gave, after column chromatography on silica get eluting with light petroleum ether–ether (19:1) the 2,2-di(trideuteriomethyl-[^{13}C]-tetralone **31**-d_6 (0.18 g, 71%) as an oil; R_f [light petroleum (40–60°C):ether (9:1)] 0.6; ν_{max} (film)/cm 2052 (CD) and 1682 (CO); δ_H (250 MHz, $CDCl_3$) 8.05 (1 H, d, *J* 7.8, CH; Ar), 7.45 (1 H, t, *J* 7.6, CH; Ar), 7.25 (1 H, d, *J* 7.5, CH; Ar), 7.21 (1 H, d, *J* 7.5, CH; Ar), 2.99 (2 H, t, *J* 6.2, CH_2) and 1.97 (2 H, tt, $^3J_{H,H} = 6.4$ and $^3J_{C,H} = 3.8$, CH_2); δ_c (100.62 MHz, $CDCl_3$) 202.9, 143.3, 132.9, 131.4, 128.6, 127.9, 126.5, 41.1 (1 C, t, $^1J_{C,C} = 33.7$, C^{13}C), 36.4, 25.6 and 23.4

(1 C, septet [1:3:6:7:6:3:1], $^{1}J_{C,D} = 19.6$, $^{13}CD_3$) (Found MH^+, 183.1560. $C_{10}^{13}\ C_2H_9D_6O$ requires MH, 183.1567).

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