Research Article

Investigations into the regioselective deuteriation of enolates derived from silyl enol ethers and enolacetates

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Summary

Results are reported on the regioselective *C*-deuteriation of a series of enolates derived from the addition of MeLi to the related enolacetate and silyl enol ether and discussed in terms of the similarity between these methods; comments are made on the possible role of the additive, lithium *tert*-butoxide. Copyright © 2001 John Wiley & Sons, Ltd.

Key Words: deuterium; enols; isotopic labelling; ketones

Introduction

Kinetic *C*-protonation of enolates is very well documented.[1] By comparison, efficient *C*-deuteriation has proved to be far more difficult to achieve.[2] This has been partially attributed to the method chosen to generate the enolate.[3] The presence of a residual amine[4] (formed by protonation of the initial amide base) is known to lower

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D-incorporation significantly. This amine is believed to act as a competitive base, giving rise to internal proton return.[5] The generation of a less basic amine, such as hexamethyldisilylamine (HMDS) has partially solved this problem.[6] As an alternative, removal of this offending amine proton by using a double-deprotonation strategy[7] has been shown to further increase D-incorporation. From these extensive studies, it is evident that the presence of fully or partially deuteriated amines and ammonium salts do have a detrimental effect on the regioselectivity of *C*-deuteriation.[4,5]

  We have recently shown[8] that the deuteriation of 'base-free' enolates[†,9] like **3** (formed by the addition of MeLi to the silyl enol ether **2**) using Stork's original protocol[10,11] in the absence of an additional competitive base gives the carbonyl derivative, 2-methylte-tralone **1**-d_1 with near-perfect D-incorporation ([D]:[H] = 95:5; 68% yield) as shown in Scheme 1. We were interested in extending this procedure towards other enol derivatives. The use of enolacetates as related enolate precursors[13] is well documented. Simple addition of two equivalents of MeLi to the corresponding enolacetate **4** gives an equimolar mixture of the required lithium enolate **3** and lithium *tert*-butoxide **5** (Scheme 1). We had originally wondered whether the additional lithium *tert*-butoxide would cause similar problems to that of
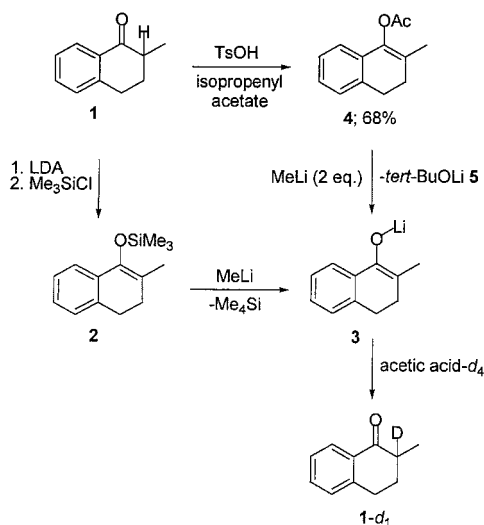
Scheme 1.

[†] They have also been termed as 'ligand-free' enolates. See Reference 9.

diisopropylamine in the regioselective deuteriation of enolates. How-ever, there are a limited number of reports[13] which suggest that this base may not directly interfere in the regioselective *C*-deuteriation step. However, the need to compare the deuteriation of enolates like **3** under both reaction conditions is important to discover the involvement of lithium *tert*-butoxide **5** in the reaction pathway.
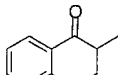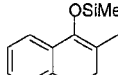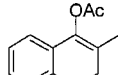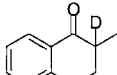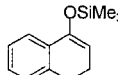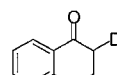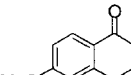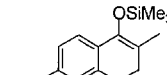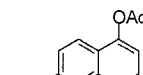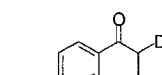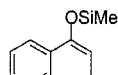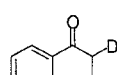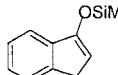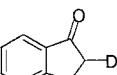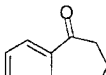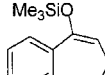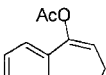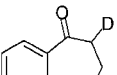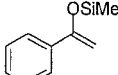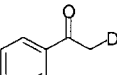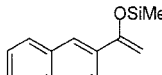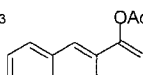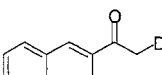
Results and discussion

We now report on this comparison, between the deuteriation of enolates derived from related silyl enol ethers and enolacetates. We discuss the use of lithium *tert*-butoxide as an additive and the possible role it plays in the deuteriation step. The required silyl enol ethers **2** and **13–19** and enolacetates **4** and **20–26** for this study were synthesized from the corresponding ketones **1** and **6–12** using well-documented procedures (Scheme 1 and Table 1).[14–16]
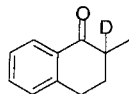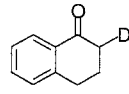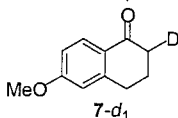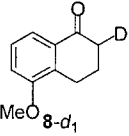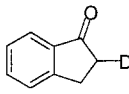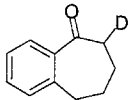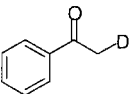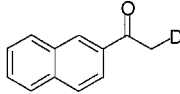
We initially probed the deuteriation of a series of 'base-free' enolates in the absence of an additive using a carbonyl directing deuterium source, such as acetic acid-d_4. The required 'base-free' enolates were formed by addition of MeLi (1.6 M in ether, 1.1 equivalent) to the corresponding neat silyl enol ethers **2** and **13–19** at room temperature. After stirring for an initial period of 5 min, THF was added and the solution was pre-cooled to -78°C. Three equivalents of the deuterium source, acetic acid-d_4 was added to give the corresponding deuteriated ketones **1** and **6–12**-d_1 in good yield with high levels of D-incorporation (Table 2).

With this information in hand, we next probed the effect of a lithium *tert*-butoxide additive **5** on this deuteriation step. Addition of two equivalents of MeLi to the related enolacetate **4** and **20–26** – under near-identical conditions to that of the silyl enol ether – followed by the addition of acetic acid-d_4 (3 equivalents) gave the same ketones **1**-d_1 and **6–12**-d_1 in a similar yield (Table 2). By comparison, the regioselective *C*-deuteriation of these related enolates, with and without a lithium *tert*-butoxide additive **5** was surprisingly similar and presumably the additional lithium *tert*-butoxide appears to play a minor role. There were a few exceptions, most notably for 6-methoxytetralone **7**-d_1 (Table 2: entry 3) and indanone **9**-d_1 (Table 2: entry 5). However, the ques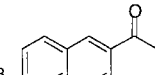tion still remained, whether acetic acid-d_4 or *tert*-butanol-d_1 **26** was the active deuteriation source in the enolacetate series (Scheme 2).

Table 1. Reported yields for the synthesis of silyl enol ethers 2 and 13–19 and enolacetates 4 and 20–26 together with NMR couplings and isotopic shifts

Entry	Starting material	Silyl enol ether	Enolacetate	Product	$^2J_{CD}$ (Hz)	Isotope shift (Hz)[26]
1	**1**	**2**; 71%	**4**; 68%	**1**-d_1	19.2	75.4
2	**6**	**13**; 82%	**20**; 76%	**6**-d_1	19.8	34.6
3	**7**	**14**; 71%	**21**; 81%	**7**-d_1	19.7	34.8
4	**8**	**15**; 71%	**22**; 82%	**8**-d_1	19.6	23.5
5	**9**	**16**; 73%	**23**; 74%	**9**-d_1	19.8	20.3
6	**10**	**17**; 70%	**24**; 58%	**10**-d_1	19.6	19.6
7	**11**	**18**; 84%	**25**; 78%	**11**-d_1	19.2	24.5
8	**12**	**19**; 72%	**26**; 86%	**12**-d_1	19.7	24.6

Table 2. Reported yields and regioselectivity in the synthesis of the ketones $1\text{-}d_1$ and $6\text{–}12\text{-}d_1$

Entry		MeLi (1.1 eq.) and acetic acid-d_4 (3 eq.) from silyl enol ether	MeLi (2 eq.) and acetic acid-d_4 (3 eq.) from acetate	MeLi (1 eq.) and tert-BuOH-d_1 (3 eq.) from silyl enol ether
1	$1\text{-}d_1$	95:5; d_1:d_0; 62%	98:2; d_1:d_0; 70%	>95:5; d_1:d_0; 68%
2	$6\text{-}d_1$	87:13; d_1:d_0; 87%	84:16; d_1:d_0; 73%	74:26; d_1:d_2; 68%
3	$7\text{-}d_1$	67:33; d_1:d_0; 79%	85:15; d_1:d_0; 83%	97:3; d_1:d_2; 78%
4	$8\text{-}d_1$	—	73:27; d_1:d_0; 85%	91:1; d_1:d_2; 74%
5	$9\text{-}d_1$	84:16; d_1:d_0; 80%	97:3; d_1:d_0; 70%	90:10; d_1:d_2; 72%
6	$10\text{-}d_1$	86:14; d_1:d_0; 85%	76:24; d_1:d_0; 78%	98:2; d_1:d_0; 70%
7	$11\text{-}d_1$	95:5; d_1:d_0; 78%	89:11; d_1:d_0; 81%	86:14; d_1:d_2; 72%
8	$12\text{-}d_1$	95:5; d_1:d_0; 85%	94:6; d_1:d_0; 71%	85:15; d_1:d_2; 78%
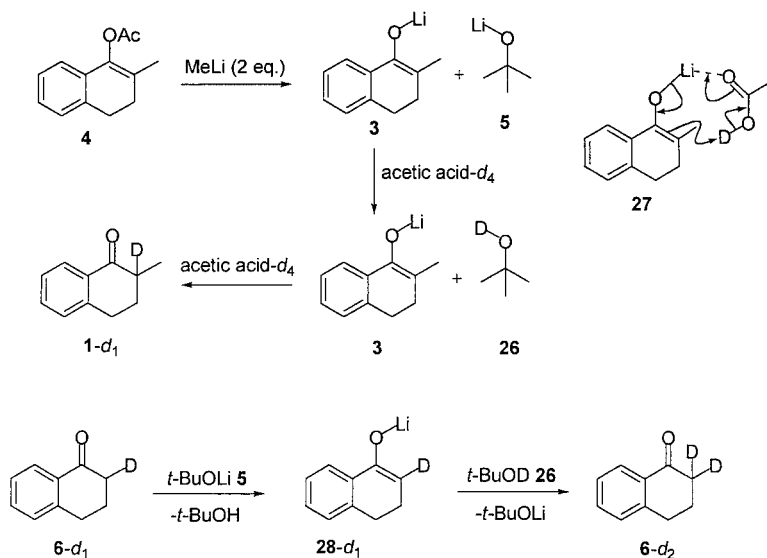
Scheme 2.

In an attempt to investigate the nature of the deuterium source present in the reaction mixture, we quenched our previous series of 'base-free' enolates (derived from the addition of MeLi to the silyl enol ethers **2** and **13–19**) with *tert*-butanol-d_1 (3 equivalents). It is clear that under these reaction conditions, selective deuteration had not occurred, and in many cases the presence of di-deuteriated ketone **6**–d_2, **11**–d_2 and **12**–d_2 was clearly evident by ^{1}H NMR. This has presumably occurred as a result of proton–deuterium exchange under basic conditions involving the by-product lithium *tert*-butoxide **5**, a ketone-d_1 (e.g. **6**-d_1), an enolate (e.g. **28**-d_1) and an excess of *tert*-butanol-d_1 **26** (Scheme 2). It is therefore not surprising that for ketones which cannot undergo proton–deuterium exchange, such as 2-methyl tetralone **1**-d_1 the D-incorporation was near perfect (Table 2: entry 1).

It is well documented that the analogous proton transfer between highly electronegative atoms such as *O*-based acids and base is at least 1000-fold faster than that between an analogous *C*-based base.[17] The initial addition of acetic acid-d_4 to the lithium *tert*-butoxide–enolate complex (e.g. **3**) must allow deuterium exchange to occur between the lithium *tert*-butoxide **5** and acetic acid-d_4 to form *tert*-butanol-d_1 **26** and the non-basic counter-acetate counter-anion (Scheme 2). The remainder of the acetic acid-d_4 must be responsible for deuterium exchange to the

enolate. Others[‡] and we[21,22] have previously postulated that such a process occurs via a chelated complex **27**.

During the course of this study, we noticed a number of characteristic features due to the presence of the deuterium atom within ketones **1** and **6–12**-d_1: (a) the presence of an infrared C–D stretching frequency[23] at approximately 2100 cm^{-1}, (b) the presence of a 1:1:1 C–D triplet (J_{C-D} 19.5 Hz)[24,25] and a negative isotope shift[20] for the C–D bond (versus the corresponding C–H bond) in the ^{13}C NMR spectra between 23 and 75 Hz (Table 1).

Experimental

Typical experimental deuteriation procedure for an enolacetate

A solution of MeLi (0.66 ml, 1.6 M in ether, 1.06 mmol) was added dropwise to the enolacetate **20** (0.1 g, 0.53 mmol) at room temperature. This resulting solution was stirred for 1 h at room temperature and then cooled at −78°C. Acetic acid-d_4 (0.12 g, 1.59 mmol) in THF (1 ml) was added dropwise to this solution and the mixture stirred for a further 30 min. The reaction was quenched by the addition of water (10 ml). The solution was extracted with ether (3 × 20 ml), dried (MgSO$_4$) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60°C):ether (9:1) to give the tetralone-d_1 **6** (57 mg, 73%) as an oil; R_f [light petroleum (40–60°C):ether (9:1)] 0.3; v_{max} (film)/cm^{-1} 2106 (C–D) and 1683 (CO); δ_H(250 MHz, CDCl$_3$) 8.00 (1 H, d, J = 7.7 Hz, CH; Ar), 7.47 (1 H, dd, J = 7.7 and 7.6 Hz, CH; Ar), 7.30–7.20 (2 H, m, 2 × CH; Ar), 2.95 (2 H, t, J = 6.1 Hz, CH$_2$CH=C), 2.60 (1 H, m, CHD) and 2.20–2.10 (2 H, br q, J = 6.1 Hz, CH$_2$CHD); δ_C(62.5 MHz, CDCl$_3$) 199.4, 144.5, 133.4, 132.7, 128.8, 127.2, 38.9 (1 C, t, J = 19.6 Hz, CHD), 29.7 and 23.6 (found MH$^+$, 148.0873. C$_{10}$H$_{10}$DO requires MH, 148.0878); m/z 148.1 (100%, M + H). The isotopic shift was 34.9 Hz.

Typical experimental deuteriation procedure for a silyl enol ether

A solution of MeLi (0.31 ml, 1.6 M in ether, 0.50 mmol) was added dropwise to the silyl enol ether **13** (0.1 g, 0.45 mmol) at room

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[‡]Others report on the use of carbonyl chelation proton donors; see References 18–20. For a recent review, in this area see Reference 3.

temperature. This resulting solution was stirred for 1 h at room temperature and then cooled at $-78°C$. Acetic acid-d_4 (0.1 g, 1.35 mmol) in THF (1 ml) was added dropwise to this solution and the mixture stirred for a further 30 min. The reaction was quenched by the addition of water (10 ml). The solution was extracted with ether (3 × 20 ml), dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60°C):ether (9:1) to give the tetralone-d_1 **6** (57 mg, 87%) as an oil, identical to that obtained previously.

Acknowledgements

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