

Methyl exchange on silicon during the addition of methylmagnesium iodide to a cyanohydrin *O*-silyl ether

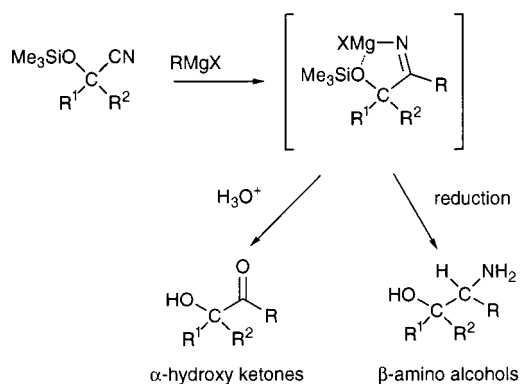
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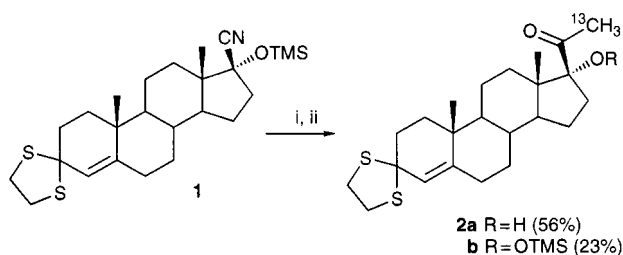
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Reaction of [^{13}C]methylmagnesium iodide (99 atom% ^{13}C) with cyanohydrin *O*-trimethylsilyl ether **1**, followed by acidic hydrolysis, led to the formation of a methyl ketone derivative **2a** that was only partially labelled (60 ± 5 atom% ^{13}C); this loss of labelling occurred through a methyl exchange reaction on silicon as shown by the presence on intermediate **2b** of [^{13}C]methyl groups on silicon (30 atom% ^{13}C).

The addition of Grignard reagents to cyanohydrin *O*-silyl ethers is a highly efficient method for synthesising α -hydroxy ketones^{1,2} or β -amino alcohols^{1,3} (Scheme 1). This reaction which has found numerous applications in the synthesis of natural products,^{4–6} provides easy access to type **2** α -hydroxy ketones from cyanohydrin *O*-trimethylsilyl ether **1**.



During studies of the allergenic potential of corticosteroids^{7,8} and their interactions with skin proteins by ^{13}C NMR spectroscopy, we were interested in the synthesis of the [$^{21-13}\text{C}$] intermediate **2**. Addition of 2.2 equiv. of [^{13}C]methylmagnesium iodide (99 atom% ^{13}C) to **1** in toluene– Et_2O (4 : 1) at 60 °C for 26 h, followed by acidic hydrolysis, gave a mixture of **2a** and **2b** (Scheme 2) with a combined yield of 79%. However, ^1H NMR analysis of these products gave surprising results. In addition to the expected doublet at δ 2.25 ($J_{\text{C-H}} = 128$ Hz) which confirmed the formation of a [^{13}C]methyl ketone, a singlet at δ 2.25 was seen accounting for $40 \pm 5\%$ of the ^1H



Scheme 2 Reagents and conditions: i, $^{13}\text{CH}_3\text{MgI}$, Et_2O , toluene, 26 h, 55–60 °C; ii, HCl 10%, acetone, THF, 14 h, room temp.

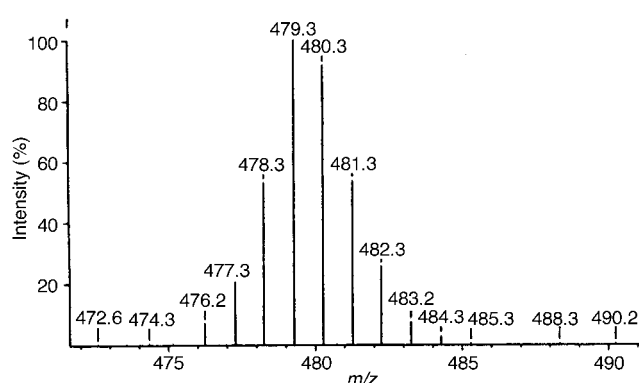


Fig. 1 Mass spectrum of compound **2b** (molecular peak).

integration and due to the presence of [^{12}C]methyl ketone. Moreover, in addition to the expected singlet at δ 0.1, and characteristic of methyl groups on silicon (compound **2b**), we observed a doublet ($J_{\text{C-H}} = 118$ Hz) which is consistent with the presence of [^{13}C]methyl groups on silicon.

This clearly indicates that the 21-methyl position was only partially labelled (60 ± 5 atom% ^{13}C) and that some methyl groups on silicon were also partially labelled (30 atom% ^{13}C). A mass spectrum of compound **2b** (electronic impact, Fig. 1) confirmed this finding and showed an almost statistical distribution of [^{13}C]methyl groups on the molecule.⁹

Addition of Grignard reagents to nitriles proceeds *via* rapid nitrogen complexation, followed by a slow addition of the alkyl group, to form an intermediate imine.^{10–12} The presence of 30 atom% ^{13}C on the silyl group indicated that 0.9 equiv. of methyl had been exchanged. If this process occurred before the addition reaction on the nitrile, this would lead to a 1.3 : 0.9 mixture of $^{13}\text{C}/^{12}\text{C}$ on the Grignard and therefore to 60 atom% ^{13}C labelling of the methyl ketone.

Thus, our finding could support the idea of a methyl exchange reaction occurring before the Grignard reagent addition on the nitrile, even if we do not know the effect of a potential complexation of methyl magnesium iodide with trimethylsilyl ether on this exchange process.

Notes and references

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- 9 *M* calculated for C₂₆H₄₂O₂S₂Si: 478.24.
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