A Novel Mechanism for the Conversion of α-Cyclopropylbenzyl Alcohol into γ-Trimethylsilylbutyrophenone

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Mechanistic studies of the reaction between α-cyclopropylbenzyl alcohol and methyl-lithium followed by hexamethyldisilane indicate that disproportionation of intermediate (**4**) with trimethylsilyl anion as catalyst provides cyclopropyl phenyl ketone; *in situ* 1,4-addition of trimethylsilyl anion to the latter compound leads to the major product, γ-trimethylsilylbutyrophenone (**2**).

Many electrophilic reagents contain a moiety which can act only as a leaving group when the reagent is attacked by a nucleophile (A). However, when certain reagents 'RL' (L = leaving group) undergo nucleophilic attack by A, 'L' reattacks the stable intermediate AR, and so two reactions occur in one pot. These compounds, RL, can be called 'counterattacking reagents,' and their use facilitates functional group transformations.

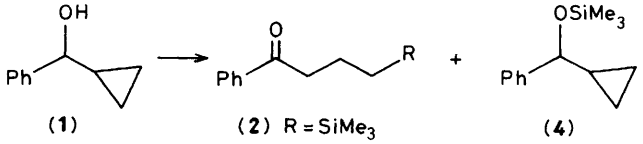
During our investigation of silicon-containing counter-attacking reagents,[1] we found that α-cyclopropylbenzyl alcohol (**1**) can be converted into γ-trimethylsilylbutyrophenone (**2**) *via* an unusual pathway. Mechanistic studies which we now discuss show that a novel disproportionation process was occurring.

α-Cyclopropylbenzyl alcohol (**1**) in hexamethylphosphoramide (HMPA) was stirred with methyl-lithium (1.1 equiv.) in ether at 0 °C for 15 min under argon. Hexamethyldisilane (1.1 equiv.) was added, the mixture stirred for 30 min at 0 °C then carefully heated with stirring to 110 °C (the ether boiled off), and maintained at this temperature for 48 h. Aqueous workup of the brown mixture followed by purification by medium pressure liquid chromatography afforded (**2**) (44%), (**3**) (22%), and (**4**) (18%)† (Scheme 1).

This one-pot cyclopropyl ring opening procedure is a feasible route to some γ-trimethylsilyl ketones. However, several processes may be responsible for the conversion of (**1**) into (**2**), an insight into which would be essential for stereochemical control of this process with more complicated substrates, and also for an understanding of the basic character of the trimethylsilyl group and the cyclopropylmethanol system.

Our results indicate that the mechanisms depicted in Scheme 2 can account for the formation of compounds (**2**)—(**4**) from (**1**). We suggest that the alkoxide (**5**) attacks hexamethyldisilane to give compound (**4**), with concomitant formation of Me_3Si^-, which may abstract acidic protons from substrates.[2] If Me_3Si^- counterattacks the benzylic proton in (**4**), the resulting anion (**6**) may fragment to generate cyclopropyl phenyl ketone (**7**). Indeed, disproportionation of the benzyl silyl ether (**4**) with a slight excess of trimethylsilyllithium, prepared by Still's procedure,[3] provided (**7**) (96%) at room temperature. Me_3Si^- is regenerated in the reaction to give (**7**), and so its function is catalytic; treatment of (**4**) with a catalytic amount of Me_3Si^- (8.5 mol %) smoothly afforded (**7**), although in lower yield (51%) after a longer reaction time (120 h). Hence, it is possible to oxidize trimethylsilyl ethers[4] possessing acidic protons at the α position to the corresponding ketones using Me_3Si^- as a catalyst.

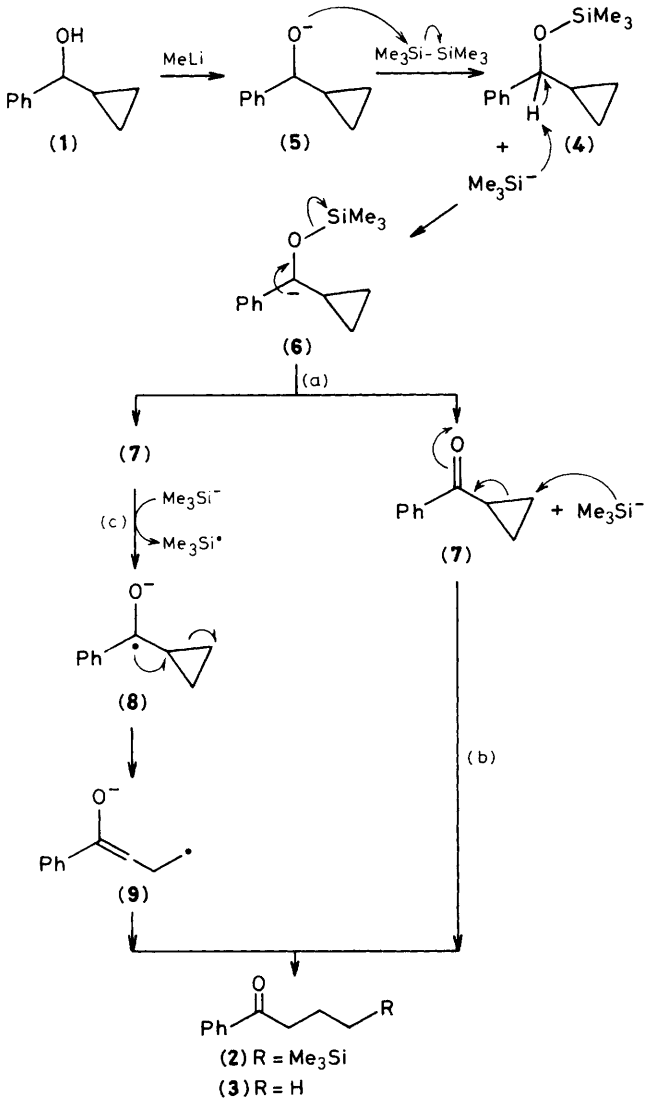
Further proof of this base-initiated disproportionation was obtained in the reaction of (**4**) with Bu^sLi. After 2 h at 110 °C,



(**1**) (**2**) R = $SiMe_3$ (**3**) R = H (**4**)

Scheme 1

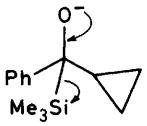
† Identified by chromatographic as well as i.r., n.m.r., and mass spectral comparison with an authentic specimen.



Scheme 2

(7) was obtained (34%), along with (1) (58%). The recovery of a larger quantity of (1) when Bu^{s}Li was used as the base indicated that Me_3Si^- is superior to Bu^{s-} for abstraction of acidic protons in the presence of the trimethylsilyloxy group.

Two routes are possible for the desilylation of (6) to (7). In addition to pathway (a), involving cleavage of the O–Si bond, cleavage of the C–Si bond in the oxyanion (10) of the corresponding α-silyl alcohol, resulting from silyl-Wittig rearrangement of (6), is also possible. Reaction of α-(trimethylsilyl)benzyl alcohol, the equilibrium for which in the presence of alkali metal reagents favours the oxyanion,[5] with Bu^{s}Li (1.1 equiv.) in HMPA at room temperature for 24 h did not generate any benzaldehyde. Therefore, the unprecedented C–Si bond cleavage did not occur. On the other hand, reaction of (diphenylmethoxy)trimethylsilane under the same conditions provided benzophenone (22%), as well as benzhydrol (56%) and unchanged methoxysilane (16%). The equilibria for deprotonated (diphenylmethoxy)silane systems are known to lie far towards the carbanions.[5,6] As further support for pathway (a), the same type of β-elimination of α-carbanions of alkyl ethers, affording ketones, is well known.[7] To our knowledge, the desilylations for (6) and the carbanion of (diphenylmethoxy)trimethylsilane are the first



examples of Me_3Si^- behaving as a leaving group in a silyl ether system.

Reaction of (7) with trimethylsilyl-lithium in HMPA at 110 °C gave (2) (42%) and (3) (24%), yields which are comparable to those for the reaction of (1) (Scheme 1). This 1,4-addition of trimethylsilyl-lithium with cyclopropyl ketones provides a simple route to γ-trimethylsilyl ketones.

It is well known that trimethylsilyl-lithium can transfer one electron to a substrate to give the trimethylsilyl radical.[8] The radical anion (8), from (7) and Me_3Si^-, could give a ring-opened product, the primary radical anion (9), as shown in pathway (c). Trapping of hydrogen by (9) during workup would provide (3). The reaction of (7) with a preformed mixture of naphthalene radical anion and $Me_3Si\cdot$, prepared by the Sakurai procedure,[8] gave (3) (11%), supporting path (c). The combination of (9) with $Me_3Si\cdot$ also provided (2), but in low yield (14%). It is more likely that the major route to (2) involves a Michael-type reaction, *i.e.* pathway (b). The mechanism for the reaction shown in Scheme 1 thus involves pathway (a) followed by (b) and (c).

Other possible pathways for the formation of (3) and (4), including anionic hydride shift, [1,4] thermal or [1,5] anionic migration of the Me_3Si group, and alternative radical mechanisms have been eliminated; details will be published elsewhere.

Our results have indicated the unusual properties of the trimethylsilyl ether intermediate (4) and have shown that: (i) the leaving group Me_3Si^- in the 'counterattacking reagent,' hexamethyldisilane, can backattack to remove an acidic proton from the reactant (4), so the oxidation of (1) to (7) can be carried out in one pot under basic conditions; (ii) Me_3Si^- has advantages as a proton abstractor; (iii) a new route to γ-trimethylsilyl ketones is available.

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