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Reactions of phenyldimethylsilyllithium with β-*N*,*N*-dimethylaminoenones

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Phenyldimethylsilyllithium reacts with the β-*N*,*N*-dimethylaminoenones 1 and 7, with the enal 5, and with ethyl β-*N*,*N*-dimethylaminoacrylate 9 to give the corresponding α,β-unsaturated carbonyl compounds with a β-phenyldimethylsilyl group, but in the last case only when the reaction mixture is given a mysteriously brief treatment with methyl iodide before workup.

In the preceding communication[1]and its predecessors,[2–4] we described several remarkable reactions of the phenyldimethylsilyllithium reagent with *N*,*N*-dimethylamides. In this communication we describe the somewhat less surprising reactions with four of their vinylogous counterparts.

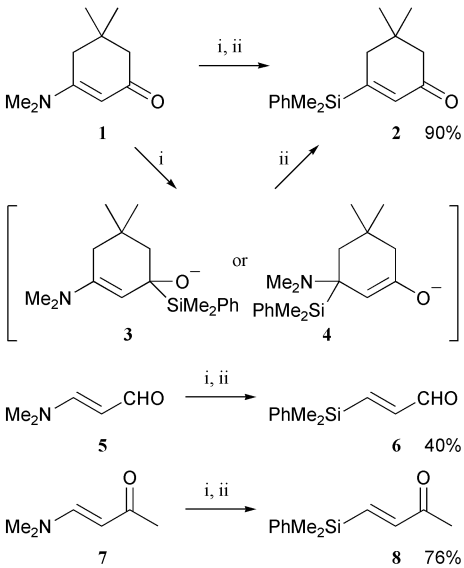
The reaction with the enone **1** was unexceptional in giving overall substitution of the dimethylamino group by the silyl group (Scheme 1). Two pathways might have been followed. In one, the silyllithium reagent attacked the carbonyl group directly to give the enamine **3**, hydrolysis of which, followed by elimination of water, would give the enone **2**. Alternatively, conjugate attack took place to give the enolate **4**, which underwent elimination of the dimethylamino group. A similar outcome was found for the enal **5** giving the enal **6**, in a less clean reaction with the same two possible pathways. The conjugate addition–elimination pathway is certainly followed in the reaction between the silyllithium reagent and the enone **7**, which gave the β-silylenone **8** in good yield. Furthermore, it is known that a β-amino group encourages conjugate addition by organolithium reagents,[5] and trimethylsilyllithium is also known to give conjugate addition, rather than direct attack at the carbonyl group, with cyclohexenones.[6] Finally, it is not obvious why the pathway involving direct attack at the carbonyl group should not enter the carbene-forming sequence that we have seen is so accessible in the reactions described earlier.[1–4] It seems likely that the conjugate addition–elimination pathway is followed in all of these reactions.

In any case, the products **2**, **6** and **8** are easily made by other methods,[7–9] and so we have not taken this investigation any further. Instead we investigated the corresponding reaction with the vinylogous carbamate **9**, which gave us a curious result, and a better synthesis of the ester **12** than the one we had been using hitherto in our synthetic work

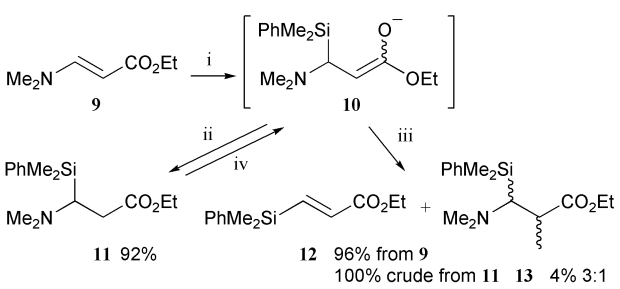
When we added the silyllithium reagent to the ester **9** and quenched with sodium bicarbonate solution, the only product was that of conjugate addition, **11** (Scheme 2). While this is an unsurprising result in itself, it raised the first question: why was the dimethylamino group eliminated in the experiments in Scheme 1, and not here? One possibility is that the ketone and aldehyde enolates are kinetically protonated on oxygen. The resultant enols might then live long enough to expel the dimethylamino group in the protic medium before they underwent tautomerism to the ketones or the aldehyde. In contrast, it is possible that the ester enolate is protonated directly on carbon, and the dimethylamino group would not then be easily lost.[10]

However, this was not the most puzzling observation. If, instead of the aqueous quench, we added methyl iodide, and then worked up in the usual way, the major product was the β-silylester **12**. This was not the result that we expected, because the enolate ion in the intermediate **10** ought to have been more nucleophilic towards methyl iodide than the dimethylamino group. The product of enolate methylation **13** was detectable only in small amounts. Similarly, when we regenerated the enolate **10** from the ester **11** using LDA, and treated that enolate with methyl iodide, the same unsaturated ester **12** was formed.

Additionally remarkable is that the elimination of dimethylamine **10** → **12** achieved by the treatment with methyl iodide took only 10–20 min at −20 °C. In contrast, if we treated the amine **11** with methyl iodide in THF at room temperature, little *N*-methylation took place over 18 h—we recovered the amine **11** in 86% yield. Evidently, the α-silyl group does not on its own increase the nucleophilicity of the nitrogen lone pair[11] enough to account for the ease of *N*-methylation, and we have no convincing explanation for the ease with which the elimination took place. It is not specific to using methyl iodide, since benzyl chloride and allyl bromide had the same effect, although not in such good yield. The most obvious explanation would have



Scheme 1 *Reagents and conditions*: i, $PhMe_2SiLi$, −78 °C, 1 h, −20 °C 1 h; ii, $NaHCO_3$, H_2O.



Scheme 2 *Reagents and conditions*: i, $PhMe_2SiLi$, THF, −78 °C, 2 h,−20 °C 1 h; ii, $NaHCO_3$, H_2O; iii, MeI, 10–20 min; iv, LDA, THF, −78 °C.

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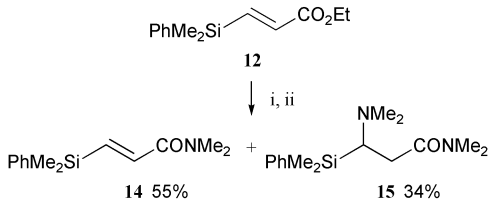
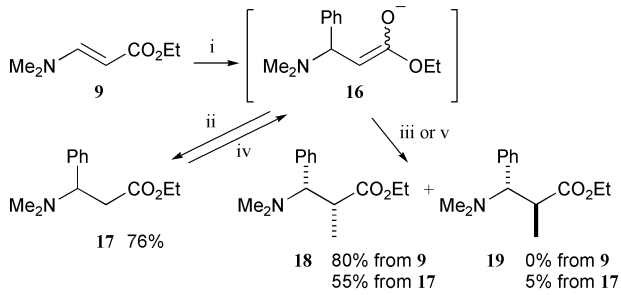
been that the dimethylamide ion had already been expelled from the enolate **10** before the aqueous quench, and had added back during the aqueous quench. The role of the methyl iodide in this scenario would have been to quench the dimethylamide ion, and prevent it from adding back. This is not the explanation, because the unsaturated ester **12**, which would have been the product of that elimination, reacted with lithium dimethylamide to give the amides **14** and **15** (Scheme 3). These products were not present in the reaction mixtures from Scheme 2. Furthermore, quenching the reaction mixture from the conjugate addition by injecting it directly into aqueous hydrochloric acid gave largely the ester **11** (67%) and only a little (9%) of the product of elimination **12**.

The easy elimination induced by methyl iodide has something to do with the presence of the silyl group. We repeated the reaction with the ester **9** using phenyllithium instead of phenyldimethylsilyllithium (Scheme 4). Conjugate addition took place to give the enolate **16**; quenching with ammonium chloride solution gave the amino ester **17**; but quenching with methyl iodide gave the expected enolate methylation, with the expected[12] high degree of diastereoselectivity in favour of the known[13] isomer **18**.

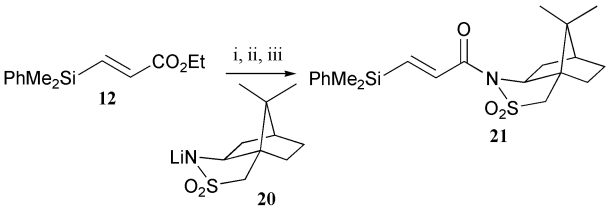
The ester **12** has usually been prepared most economically by hydrosilylation–dehydrogenation of ethyl acrylate,[14] but in that otherwise excellent method it is always contaminated with the saturated analogue, no matter how much of an excess of ethyl acrylate is used to limit the amount of hydrosilylation. In our experience, removing the saturated analogue has frequently been difficult, while the new synthesis reported here is free of this problem. For further development, it was helpful to saponify the crude ester **12**, in order to separate acidic products from silicon-containing byproducts. The carboxylic acid occasionally crystallised, but recrystallisation, either of the acid or of its various salts was not practical. Since we needed it attached to Oppolzer's auxiliary, as did he,[15] we converted the acid into its acid chloride and joined it onto the auxiliary (Scheme 5), at which point we had a crystalline derivative **21** that could be purified by recrystallisation. The overall yield of this useful compound from the amino ester **9** was 41%.



Scheme 3 *Reagents and conditions*: i, Me_2NLi, THF, −78 °C, 0.5 h, −20 °C, 1 h; ii, $NaHCO_3$, H_2O.



Scheme 4 *Reagents and conditions*: i, PhLi, Et_2O, −10 °C, 0.5 h, rt, 1 h; ii, NH_4Cl, H_2O; iii, (from **9**) MeI, 15 h; iv, LDA, THF, −78 °C; v, (from **17**) MeI, −78 °C, 0.5 h, rt, 1 h.



Scheme 5 *Reagents and conditions*: i, KOH, MeOH, H_2O, rt, 1.5 h; ii, $(COCl)_2$, DMF, CH_2Cl_2, rt, 1 h; iii, **20**, THF, −78 °C, → rt, 1 h.

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