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The reaction of phenyldimethylsilyllithium with *N*-phenylpyrrolidone

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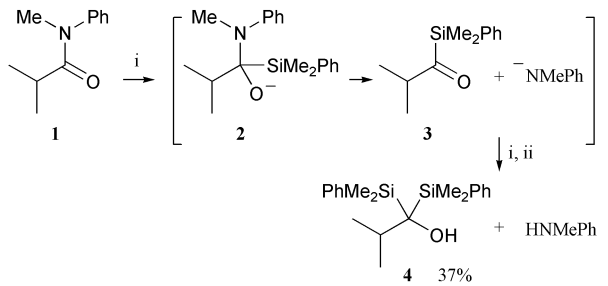
Phenyldimethylsilyllithium reacts with *N*-phenylpyrrolidone 5 to give the known tetracyclic amines [2,3,3*a*,3*b*,4,5,6,11*b*-octahydro-3*aα*,3*bα*,11*bα*-1-phenyl-1*H*-dipyrrolo(1,2*a*:3′,2′*c*)quinoline and its 3*bβ* isomer] 6 and 7.

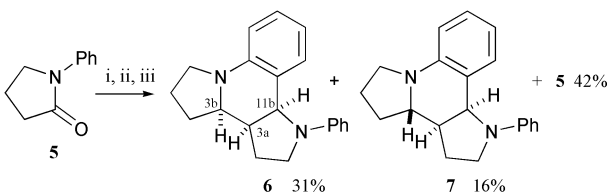
Whereas phenyldimethylsilyllithium reacts with *N*,*N*-dialkylamides to give a variety of unexpected products,[1] we find that the reaction with the *N*-phenylamide **1** is more straightforward (Scheme 1): the tetrahedral intermediate **2** breaks down by expulsion of the *N*-methylanilide ion before any of the more surprising events takes place. The acylsilane **3** so formed is attacked by another equivalent of the silyllithium reagent to give the known disilyl alcohol **4**.[2] We had a similar experience with *N*,*N*-dialkylthioamides, except that the corresponding thioacylsilanes enolised, instead of being attacked by a second equivalent.[3]

We reasoned that if the nucleofugal amide ion were tied to the rest of the molecule, it might return in the sense **3** → **2**, and allow one or more of the Brook-rearrangement and carbene-based reactions that we had seen earlier take place. Accordingly, we treated *N*-phenylpyrrolidone **5** with the silyllithium reagent, and obtained as the major products the two tetracyclic amines **6** and **7** (Scheme 2). Clearly we had succeeded in tapping into another remarkable sequence of reactions.

These two compounds are well known,[4–9] and our products were identical with authentic samples prepared by one of the literature procedures.[4] The relative stereochemistry, although correctly assigned,[4] had not been proved. We obtained X-ray crystal structures† for both compounds, which confirm their structures, and prove that the major product, with the higher melting point, has the 3*bα* stereochemistry **6** relative to 3*aα* and 11*bα*.



Scheme 1 *Reagents and conditions*: i, 2.4 equiv. $PhMe_2SiLi$, −78 °C; ii, $NaHCO_3$, H_2O.

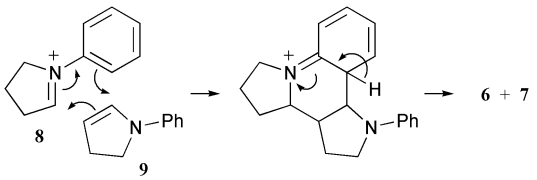


Scheme 2 *Reagents and conditions*: i, 2.4 equiv. $PhMe_2SiLi$, −78 °C; ii, warm to –20 °C; iii, $NaHCO_3$, H_2O.

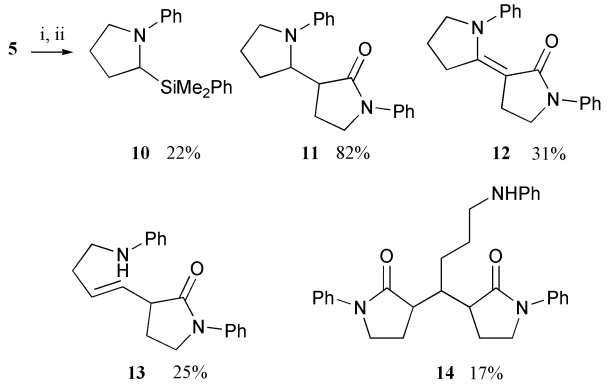
Some of the literature procedures are based on reduction of the lactam **5**, notably that using lithium aluminium hydride.[4,8] Others are based on the oxidation of the corresponding pyrrolidine, using such reagents as diethyl azodicarboxylate,[6] ozone,[6] irradiation with gamma rays[7] and *tert*-butoxy radicals.[7] The key step in the mechanism suggested in the literature[4,6] is a Diels–Alder reaction (Scheme 3) between the iminium ion **8** and the enamine **9**, both of which have oxidation states between that of the pyrrolidone and that of the pyrrolidine. The major isomer **6** corresponds to the *endo* product, which was the basis for the earlier assignment of relative configuration.

Given the ease and the variety of ways with which the products **6** and **7** can be formed, they must represent a deep hole on the energy surface, or at any rate there must be a deep valley leading to them.[10] Nevertheless, the mechanism in Scheme 3 did not seem to be compatible in detail with our reaction conditions. In particular, we could not see how the iminium ion could be formed in aprotic conditions, and then survive long enough to react with the enamine in a solution containing an excess of the powerful nucleophile, phenyldimethylsilyllithium. We therefore varied the reaction conditions and the stoichiometry, searching for evidence of intermediates that might help us to a better understanding. Without going into detail, we isolated more or less of each of the compounds **10**–**14** illustrated in Scheme 4 with the highest yield for each, one of them **11**[11] quite high, and that a plausible intermediate, since it reacted with the silyllithium reagent to give the same mixture of products **6** and **7**.

In all of these reactions, we always obtained a large amount, up to 42%, of unchanged pyrrolidone **5**. This was clearly present in the reaction mixture as its enolate, since it gave the *C*-



Scheme 3



Scheme 4 *Reagents and conditions*: i, $PhMe_2SiLi$, THF, various conditions; ii, $NaHCO_3$, H_2O.

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methylated product when we quenched with methyl iodide. Although the silyllithium reagent is usually a better nucleophile than a base, it is hardly surprising that it deprotonated some of the starting material, and that some of the resultant enolate survived until the workup.

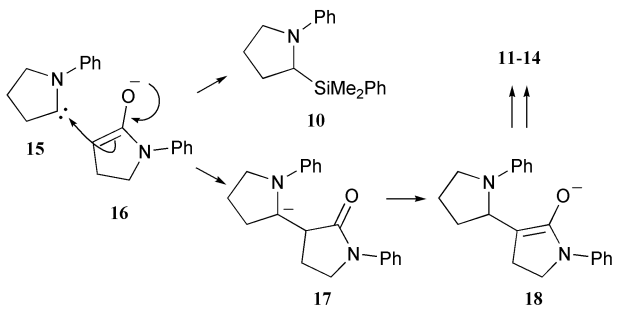
The α-silylamine **10** is the normal product for a reaction taking place between a tertiary amide and two or more equivalents of the silyllithium reagent.[1] Its formation suggests that, at least in part, the reaction is taking the pathway involving Brook rearrangement, and the formation of a carbene or carbenoid **15**. The formation of the lactam **11** can be explained if the carbene **15**, in addition to reacting with the silyllithium reagent to give the α-silylamine **10**, reacts with the enolate **16** to give the anion **17** (Scheme 5).

The only problem with this suggestion was that we had been unable in our earlier work[1] to trap a carbene intermediate using an enolate ion—the Brook-rearranging nucleophile intervened, giving an enediamine. However, that work had used ketone-derived and ester-derived enolates, and so we carried out the model reaction between our usual amide **19** and the enolate ion **16** (Scheme 6). This time we were able to isolate the product **20**, although not in high yield. Presumably the more nucleophilic enolate derived from a lactam was able to compete with the Brook-rearranging nucleophile.

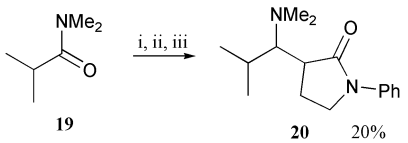
The anion **17**, by proton loss and gain, can rearrange to the enolate **18**. Elimination of the anilide group, and other straightforward steps, can account for the formation of the products **11**–**14**. It can equally account for the formation of the tetracyclic amines **6** and **7**, if the lactam **11** forms another carbene with the silyllithium reagent. The steps between the enolate **18** and the byproducts **13** and **14** supply the protons, which are needed only in catalytic amounts, to give the lactam **11** from the lithium reagent **17** and the enolate **18**.

The final intermediate before the quench must be an organolithium reagent, but we have been unsuccessful in pinning down its details. The work-up with methyl iodide mentioned above did not give us recognisable methylation products derived from the organolithium reagent, merely giving us a much lower yield of the products **5** and **6** themselves. In one run, we did isolate in 43% yield the *C*-methyl derivative **21** derived from the enolate **18**, together with the product from *C*-methylation of the starting lactam **5**.

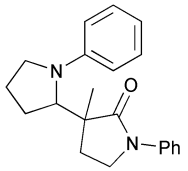
We have only established the outline of a possible mechanism. Our mechanism cannot be involved in the earlier preparations of the tetracyclic amines **6** and **7**, although they were formed, in 30 and 7% yield, respectively, when we treated the lactam **11** with lithium aluminium hydride, indicating that it could be an intermediate in that case. We have not pursued the



Scheme 5

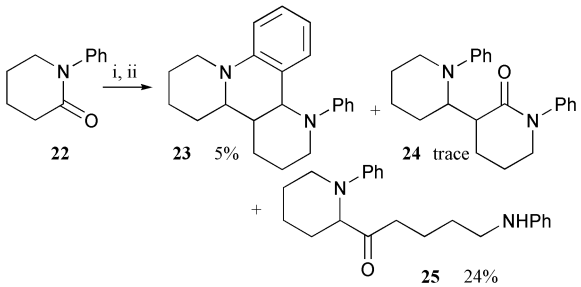


Scheme 6 *Reagents and conditions*: i, $PhMe_2SiLi$, THF, −78 °C; ii, **16**, THF, −78 °C, derived from **5** with LDA, then → −20 °C, 1 h; iii, $NaHCO_3$, H_2O.



21

details any further, since this is far from being a general reaction. With the corresponding β-lactam, ring opening was the only detectable pathway, and with the corresponding piperidone **22** (Scheme 7), the yield of the analogous tetracyclic products **23** was low, a product **24** analogous to the intermediate **11** barely recognisable, and the major product was the ketone **25**, derived by hydrolysis of the enediamine.



Scheme 7 *Reagents and conditions*: i, $PhMe_2SiLi$, THF, −78 °C, warm to −20 °C; ii, $NaHCO_3$, H_2O.

We thank the EPSRC for a maintenance award (M. B.) and for support in purchasing the Nonius CCD diffractometer, Dr J. E. Davies for determining the X-ray structures, and Dr Matthew Russell for the experiment in Scheme 6.

Notes and references

† CCDC 199968 and 199969. See http://www.rsc.org/suppdata/cc/b2/b210445h/ for crystallographic data in CIF or other electronic format.

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10 We predict that treatment with samarium iodide will almost certainly provide yet another route.

11 A mixture of diastereoisomers, the major crystalline, and known: A. K. Bocz, *Chem. Ber.*, 1966, **99**, 1923, as also is the aldol product **12**: H. Eilingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.*, 1960, **72**, 836; K. H. Büchel, A. K. Bocz and F. Korte, *Chem. Ber.*, 1966, **99**, 724.