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Reaction of 2-trifluoroacetyl-1,8-Bis(dimethylamino)naphthalene with strong organic bases: Deprotonation of 1-NMe_2 group resulting in the formation of Benzo[g]indole derivatives versus nucleophilic addition to C═O group

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ABSTRACT

A novel approach to pyrrole ring closure in 2-trifluoroacetyl- and 2-ethoxycarbonyl-1,8-bis(dimethylamino)naphthalenes via treatment with 2-lithium-1,8-bis(dimethylamino)naphthalene producing the corresponding benzo[g]indole derivatives, was examined with different alkyl- and aryllithium compounds as well as with LDA. It was found that the highest yields of benzo[g]indoles (up to 70%) are obtained with aryllithium reagents when they contain NMe_2 group in *ortho*-position to the carbanionic centre. In all other cases the formation of acyclic alcohol arising from ordinary intermolecular addition of the carbanion to the C═O group strongly prevails. The dramatic facilitation of deprotonation of the N-Me group in substrate followed by pyrrolic cyclization in the case of 2-lithium-N,*N*-dimethylanilines was explained through a specific structure of the reaction transition state.

1. Introduction

In view of the immense importance of indoles in Nature and in the different spheres of human activity[1] in conjunction with the rapid development of new synthetic procedures, the last 15 years have seen the elaboration of dozens of new methods for indole synthesis.[2] Most modern synthetic approaches to indoles are based on coupling various aniline and acetylene derivatives in the presence of appropriate transition metal catalysts. This usually provides atom- and step-economy protocol as well as nearly unlimited possibilities for indole functionalization. More surprising, quite simple and even obvious schemes remain unrealized. As an example, the pyrrole ring closure through intramolecular nucleophilic addition of α-aminomethyl carbanion **2** to *ortho*-carbonyl- or cyano- derivatives of *N*,*N*-dimethylanilines can be mentioned (Scheme 1). Two main reasons seem to be responsible for the difficulties of this method. The first one is a considerable destabilization of α-aminomethyl carbanions caused by electrostatic repulsion of neighbouring free electron pairs on nitrogen and carbon atoms (for a review on α-aminomethylcarbanions see Ref. [3]). Indeed, there were registered no signs of their formation, for example, on treatment of *N*,*N*-dimethylaniline with *n*-butyl lithium.[4] The second reason, is a lack of the strong and highly selective (low nucleophilic) bases which are needed for lithiation of C-H bond in **1** in the presence of more active C═O (C≡N) group.

Nevertheless, recently we have reported the first examples of indole synthesis based on Scheme 1.[5] In particular, we have found that treatment of 2-trifluoroacetyl-1,8-bis(dimethylamino)naphthalene **3** with 2-lithium-1,8-bis(dimethylamino)naphthalene **4a** in ether produces a mixture of benzo[g]indoles **6** and **7** along with 2,2'-binaphthyl alcohol **8a** (Scheme 2). Since **6** can be quantitatively dehydrated into **7** just by passing through a column with active SiO_2 (much worse with Al_2O_3) a total yield of benzoindole **7** is actually almost twice higher than **8a**. This means that lithium

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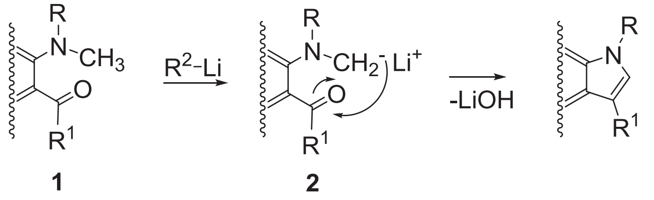
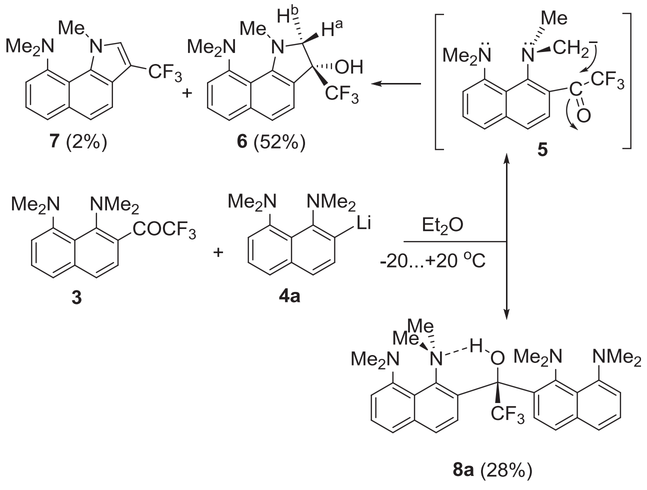


Scheme 1. Possible way of pyrrole ring closure in *ortho*-carbonyl derivatives of *N*,*N*-dimethylaniline.

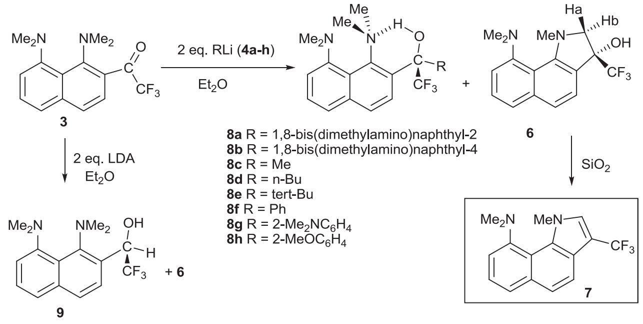
compound **4a** as a derivative of strong neutral base “proton sponge” possesses very high protophilicity and simultaneously quite moderate nucleophilicity. Our recent X-ray and solution studies of structure **4a** are in agreement with this view since **4a** exists in both media as a rather hindered dimer.[6] Following the above, the main purpose of this study consisted in using for this reaction instead of **4a** some other strong bases including alkyl- (**4c-e**) and aryllithiums (**4f-h**), as well as isomeric to **4a** 4-lithium-1,8-bis(dimethylamino) naphthalene **4b** and lithium diisopropylamide (LDA, **4i**). Thereby, we hoped to clarify factors influencing the formation of benzoindoles and to find out among these organometallic reagents even more selective protophilic reagent for the pyrrole ring closure in ketone **3**.

2. Results and discussion

In a typical experiment, ketone **3** was reacted with two equivalents of organolithium reagent **4a-i** in dry ether at −20 °C for 42 h (Scheme 3). Thereafter, the reaction mixture was poured into water, extracted with Et_2O and subjected to column chromatography on Al_2O_3. Independently, the product ratio was determined by ^1H NMR method. For this, the ethereal extract was evaporated to dryness and ^1H NMR spectrum of the residue was recorded in $CDCl_3$. The results obtained are summarized in Table 1, which also includes the calculated gas-phase proton affinity values, PA, of the tested bases. It should be noted that in the latter case no visible amount of aromatized benzoindole **7** could be found in the spectra and mainly alcohols **6** and **8** were the detectable products. However, in two experiments where *n*-BuLi and LDA were used a considerable amount of alcohol **9** was also isolated (Runs 4 and 9). Evidently, this results from reduction of **3** by the above bases, whose reducing ability is well documented in literature.[7] Though ^1H NMR spectra of crude reaction mixtures were rather complicated, it was always possible to identify the main reaction products and estimate their ratio. The simplest way is to compare characteristic signal intensities for each type of compounds: OH singlet for **8** (δ = 12.3–13.4 *ppm*), geminal CH_2(b) doublet for **6** (3.93 *ppm*) and C<u>H</u>CF_3 quartet for **9** (5.46 *ppm*). This is illustrated for runs 2 and 8 in Fig. 1.



Scheme 2. Interaction of ketone 3 with 2-lithium-1,8-bis(dimethylamino)naphthalene 4a.



Scheme 3. Interaction of Ketone **3** with Some Organolithium Compounds.

Analysis of Table 1 data leads to two main conclusions: 1) ratio of benzo[*g*]indole **6** (or **7**) to acyclic alcohols **8** strongly depends on structure of the bases used but is little sensitive to PAs values; 2) all bases in regard to ratio **6**(**7**): **8** are distinctly divided into two categories. The first one includes only aryllithium compounds **4a** and **4g**, both having NMe_2 group in *ortho*-position to carbanionic centre. They provide the largest yield of benzo[*g*]indole **7**, reaching 70% (after aromatization of **6**). All other bases constituting the second group give the benzoindole yield varying in a range 5–27%, while yields of **8** are increased to 63–95%, except *n*-BuLi and LDA where alcohol **9** prevails. We believe that these results can be interpreted in a favour of importance of the transition state structure (TSS) leading to the deprotonation of N-Me group in **3** and finally to the formation of benzoindole **6** (**7**).

Apparently, the presence of *ortho*-NMe_2 group in the bases **4a** and **4g** plays a key role. To support this we have performed DFT calculation of possible TSS with participation of **4g**. Recently, we have performed single crystal X-ray study for **4a** and found that it has dimeric structure with two molecules of Et_2O as additional ligands (Scheme 4). However, ^{13}C and ^1H NMR examination of **4a** in solution allows to conclude that under these conditions the dimer is relatively unstable (possibly due to sterics) and undergoes partial disaggregation. If so, the disaggregation of **4a** (or **4g**) in the presence of **3** might proceed with inclusion of the ketone in coordination sphere with realization of the structure close to **10** (Fig. 2). The theoretical calculation demonstrated that such structure lies in the minimum on the potential energy curve and besides it provides close enough distance (2.56 Å) between a proton of the N-CH_3 group and carbanionic centre. Additionally the coordination of Li^+ ion with the C═O group should increase the N-CH_3 group acidity simultaneously preventing the nucleophilic addition to it by keeping carbanionic centre away from the carbonyl carbon atom.

Obviously, one of the central points of this study is how wide can be applicability of the method under consideration. Unfortunately, so far we were unable to extend it to other substrates, with the exception of ester **11** and diketone **12** (Scheme 5).[5] The most attractive compounds of this type, 2-trifluoroacetyl-*N*,*N*-dimethylaniline and 2-trifluoroacetyl-*N*,*N*-dimethylnaphthalene **13a** turned out to be rather unavailable. The first of them is known to exist as a stable hydrate.[9] Synthesis of **13a** is described in the literature by 4-protodetrifluoroacetylation of diketone **13b** with CF_3CO_2H in CH_3CN/water mixture.[10] However we could not reproduce this procedure though similar preparation of **3** from **12** proceeded in