

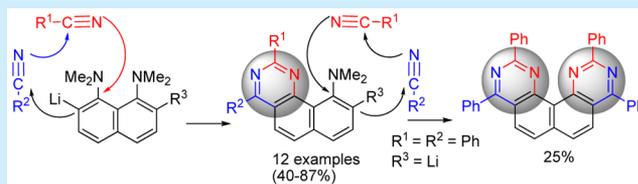
Tandem Synthesis of 10-Dimethylaminobenzo[*h*]quinazolines from 2-Ketimino-1,8-bis(dimethylamino)naphthalenes via Nucleophilic Replacement of the Unactivated Aromatic NMe₂ Group

Vladimir Y. Mikshiev, Alexander S. Antonov, and Alexander F. Pozharskii*

Department of Organic Chemistry, Southern Federal University, Zorge str. 7, 344090 Rostov-on-Don, Russian Federation

Supporting Information

ABSTRACT: It has been found that 2-bromo-1,8-bis(dimethylamino)naphthalene on sequential treatment with *n*-BuLi and 2 equiv of the same or different aryl(hetaryl) cyanide as a result of [2 + 2 + 2] nucleophilic cascade annulation produces 10-dimethylaminobenzo[*h*]quinazolines, as yet unknown NMe₂/–N= analogues of the proton sponge. It is even more convenient to use preliminarily prepared 2-ketimino-1,8-bis(dimethylamino)naphthalenes as starting material. The substitution of both *peri*-NMe₂ groups furnishing quinazolino[7,8-*h*]quinazoline derivatives is also possible. The process is remarkable by surprisingly mild nucleophilic displacement of an unactivated aromatic NMe₂ group.



Because of the extremely high basicity of the dimethylamide anion ($pK_a \approx 35$), the dimethylamino group is considered one of the worst leaving groups in nucleophilic displacement reactions. Nevertheless, there exist quite a few examples of its substitution. All of them are based on preliminary activation of the NMe₂ group via placing in a substrate molecule the strong electron-accepting functionalities (NO₂, COCF₃, etc.),¹ its conversion into an NMe₃⁺ group,² or acid catalysis.³ The two last methods allow the NMe₂ group to be eliminated in a form of relatively stable trimethyl- or dimethylammonium ions. In particular, the acid catalysis can be exemplified by our previous observation that azomethines, hydrazones, and oximes derived from 2(7)-carbonyl derivatives of 1,8-bis(dimethylamino)naphthalene (proton sponge) undergo intramolecular heterocyclizations accompanying by substitution of the 1-NMe₂ group to produce a number of difficulty accessible heterocyclic compounds and 1-naphthol derivatives.³ Herein, we report that similar cyclizations can be surprisingly and easily realized under strongly basic conditions when the NMe₂ group is formally unactivated and displaced as the Me₂N[–] anion.

The starting point for this work was our recent synthesis of unexpectedly stable 1,8-bis(dimethylamino)naphthalene-2-ketimines **2** on treatment of 2-lithium derivative **1** with various nitriles (Scheme 1).⁴ We usually employed the equimolar

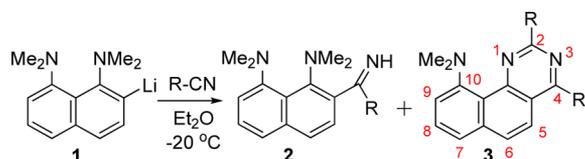
1:RCN ratio to furnish, after quenching the crude reaction mixture with water, the corresponding imine **2** in good yield. In some experiments, we also fixed by thin-layer chromatography the appearance of a yellow spot going in front of a reddish-colored zone of imine **2** (Supporting Information).

At first, we did not attach importance to this, believing that it was a small admixture of ketone, which we usually received separately and in good yield by acid hydrolysis of the corresponding imine.⁴ Nonetheless, once (in experiment with PhCN) we had studied a structure of the yellow byproduct, to our surprise, we found that it was an unknown 10-dimethylamino derivative of benzo[*h*]quinazoline **3** (R = Ph), an intriguing representative of almost unexplored *peri*-NMe₂/–N= analogues of the proton sponge. In addition, this reaction is a new synthetic way to quinazolines as an important class of nitrogen heterocycles having a considerable pharmaceutical significance.⁶

Following the most probable mechanism of the formation of **3** shown in Scheme 2, the process should involve 2 equiv of nitrile. With this point in mind, it seemed to us reasonable to begin directly from authentic imine **2** already having in its structure half of the necessary nitrile component. Accordingly, a series of **2** was treated at –20 °C with butyllithium (for bromides **2g,h** with LDA) followed by 1.1 molar equiv of the corresponding nitrile. The subsequent cyclization was conducted at room temperature.

As seen from Table 1, such a procedure provides a moderate to high yield of **3** and can be applied to a variety of aromatic and heteroaromatic nitriles (SI). Unfortunately, the method does not work for the most alkyl cyanides owing to their conversion under strongly basic conditions into a low

Scheme 1. Reaction of 2-Lithio-1,8-bis(dimethylamino)naphthalene with Nitriles



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bond. This leads to an appreciable overflow of some electron density to the imino group and even to preferable protonation of the latter over *peri*-NMe₂ groups. There are no doubts that such electron transfer in conjunction with the negative charge on terminal nitrogen atoms in imides **4** and **5** should greatly enhance nucleophilicity of the side chains.⁹ Interestingly, that one of the reviewers has suggested treating transition **5** → **6** as the 6 π -electrocyclization event, which may also help explain its facility.

We believe the rate-limiting step in conversion **2** → **3** is the formation of **5** from **4**, while the stages of nucleophilic addition **5** → **6** and aromatization **6** → **3** proceed relatively fast. In particular, this is confirmed by a strong slowing reaction at the interaction of imine **2a** with less electrophilic 4-methoxybenzotrile to produce **3b** (Figure 3, lower curve). A significant

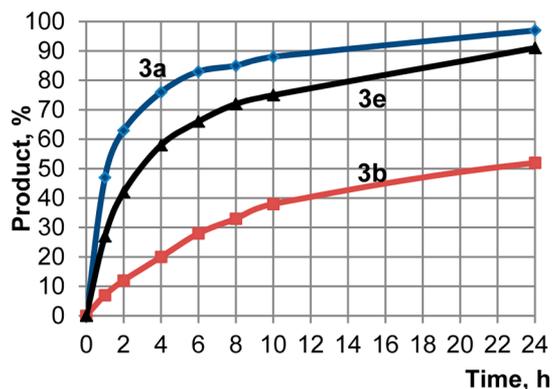


Figure 3. NMR monitoring of conversion **2** → **3** for some selected 2-ketimines.

slowdown in the process also occurs after about 50–60% conversion of **2**. We attribute this to the gradual accumulation in the reaction mixture of the dimethylamide anion, which reacts with nitrile to convert it into an amidine byproduct (experimental evidence: SI, Figure S33).

Of three aforementioned factors favoring easy nucleophilic substitution of the 1-NMe₂ group in imides **4** at their interaction with nitriles, at least two, the second and the third, stem from the proton sponge nature of the substrates. In accord with this point, we found that this reaction cannot be applied to benzene series. Thus, on treatment of 2-(dimethylamino)benzophenimine¹⁰ with *n*-BuLi and then PhCN, only the starting material was recovered from the reaction mixture. Finally, it should be noted that Li et al. have recently elaborated copper-catalyzed synthesis of quinazolines via [2 + 2 + 2] annulations of diaryliodonium salts and two nitriles.¹¹ Their approach is based exclusively on electrophilic reactions and does not address the displacement of the NMe₂ group.

In summary, it was found that interaction of 2-lithio-1,8-bis(dimethylamino)naphthalene with an excess of aryl or hetaryl cyanide proceeds as a [2 + 2 + 2] nucleophilic cascade annulation of two nitrile molecules to a naphthalene system and results in the formation of 10-(dimethylamino)benzo[*h*]-quinazoline derivatives. However, the best way for carrying out the reaction is to start from preliminarily prepared 2-ketimino-1,8-bis(dimethylamino)naphthalenes. It allows not only the use of two different nitriles but also enhances the yield of the reaction product up to 36–87%. The most innovative findings of the work are considered to be (1) a

demonstration of unusual ease of nucleophilic displacement of the formally unactivated aromatic NMe₂ group on the last stage of the process, (2) the first example of nucleophilic substitution of the two NMe₂ groups in the same substrate, and (3) a new approach to the synthesis of difficultly accessible benzo[*h*]-quinazoline derivatives. Several arguments were put forward that the success of the disclosed transformations originates from the proton sponge nature of the used substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01178.

Technical details and experimental procedures; spectral data for all new compounds (PDF)

Crystallographic data for **3a** and **3k** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: apozharskii@sfedu.ru.

Notes

The authors declare no competing financial interest.

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