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Base-promoted transformation of 2-C(O)R-1,8-bis(dimethylamino)-naphthalenes into benzo[*g*]indole derivatives

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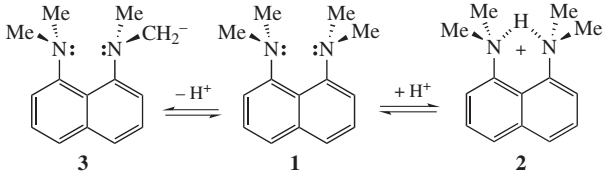
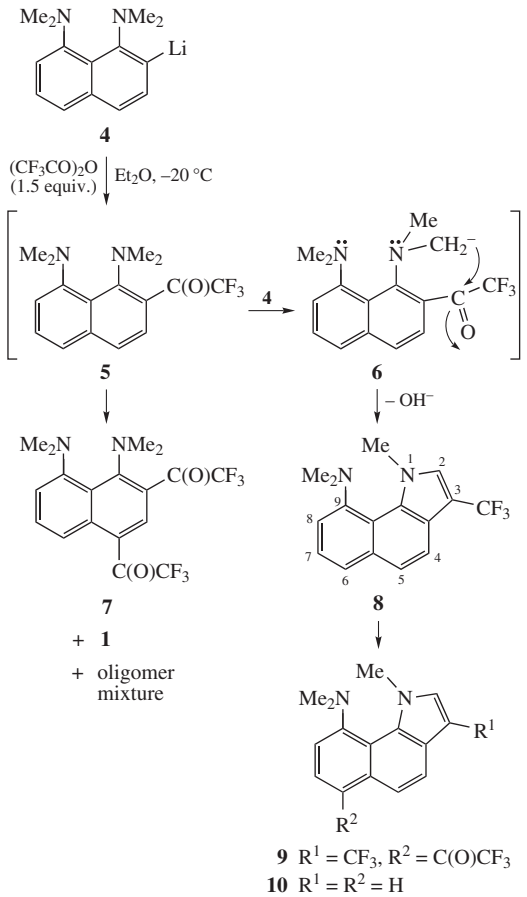
1,8-Bis(dimethylamino)naphthalenes bearing 2-positioned trifluoroacetyl or ethoxycarbonyl group on treatment with 2-lithio-1,8-bis-(dimethylamino)naphthalene undergo base-promoted transformation into benzo[*g*]indole derivatives in small to moderate yield, representing previously unknown mode of the pyrrole ring closure which proceeds *via* deprotonation of the NMe group.

Unlike the widely known abnormally high basicity (pK_a 12.1, H_2O)[1,2] of 1,8-bis(dimethylamino)naphthalene (**1**, 'proton sponge' or DMAN), a question of the CH-acidity of its NMe_2 groups until recent time has remained untouched except for a brief mention in ref. 3. A natural feeling is that acidic ionization of the methyl groups in diamine **1** should be quite unprofitable due to the destabilization of anion **3** caused by the neighboring of three unshared electron pairs.[4] Nevertheless, in the present work we report that under certain conditions NMe_2 groups in DMAN-type compounds can manifest acidic character which in some cases may be synthetically useful. Lithium derivative of DMAN **4** (Scheme 1) was the crucial reagent.



Primarily, our goal was to obtain previously unknown 2-trifluoroacetyl-1,8-bis(dimethylamino)naphthalene **5** (Scheme 1). For this purpose we treated 2-lithio-1,8-bis(dimethylamino)-naphthalene **4**[5] with 1.2–2.0 equiv. of trifluoroacetic anhydride (TFAA) in dry diethyl ether at –20 °C (Scheme 1, procedure 1).† Unexpectedly, the desired monoketone **5** was not formed. Instead, four different products **7**–**10** were isolated (along with parent **1** and red oligomers). The benzo[*g*]indole derivatives **8** and **9** (each in 5–7% yield) were of special interest. The product ratio and even their type considerably depended on the amount of TFAA used. With excess of TFAA (Table 1, runs 1–3), the starting **1**, diketone **7** and benzo[*g*]indole **8** prevailed in the reaction mixture. In contrast, on lowering TFAA (runs 4 and 5), primarily illusive monoketone **5** and indole **10** with missed 3-CF_3 group dominated among the reaction products.



Scheme 1

We believe that the formation of benzo[*g*]indoles most likely originates from the acidic ionization of the C–H bond in the

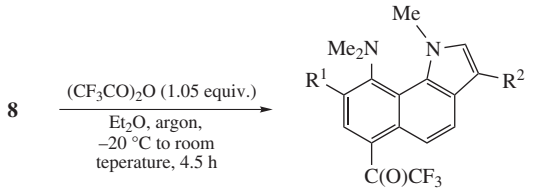
† *Procedure 1: reaction between **4** and TFAA*. BuLi solution (1.6 M in hexane, 2.1 ml, 3.4 mmol) was added under argon to a cooled to –20 °C solution of 2-bromo-1,8-bis(dimethylamino)naphthalene[6] (1 g, 3.4 mmol) in dry Et_2O (25 ml). The mixture was kept at –20 °C for 30 min and then TFAA (9.2 ml, 5.1 mmol) in dry Et_2O (20 ml) was added dropwise. After a minute the red solid precipitated from which the solvent was decanted and the solid was triturated with 30 ml of H_2O–$CHCl_3$ (1:1). Both layers were decanted from the less soluble oligomeric mixture and separated. The chloroform solution was then evaporated to a small volume and using TLC (Al_2O_3, $CHCl_3$–hexane, 1:1) diketone **7** (20 mg) was isolated as red orange crystals. The Et_2O solution was evaporated to dryness and four fractions were collected by TLC from the residue: colorless (R_f = 0.8), yellow (R_f = 0.7), orange (R_f = 0.4) and colorless (R_f = 0.2) representing compounds **8**, **9**, **7** and **1**, respectively.

Table 1 Trifluoroacetylation of **4** on variation of **4**:TFAA ratio.

Run	**4**:TFFA ratio	Product yield (%)[a]					
		1	**5**	**7**	**8**	**9**	**10**
1	1:2	20	–	14	24	2	–
2	1:1.5	15	–	35	7	6	–
3	1:1	28	–	14	10	2	–
4	1:0.5	–[b]	25	6	14	–	3
5	1:0.25	–[b]	50	3	14	–	21

[a] Preparative yields of all compounds isolated by TLC; all yields were calculated relatively to reactant taken in a smaller amount: DMAN **1** in runs 1–3 and TFAA in runs 4 and 5. [b] The yield is not indicated because much DMAN **1** (after protonation of **4**) was obtained due to excess **4**.

1-NMe_2 group of initially formed **5** under the action of highly basic **4**.[5] Thereupon, equilibrium amounts of aminomethyl carbanion **6** undergo nucleophilic cyclization at $COCF_3$ group to produce benzo[*g*]indole **8** (see Scheme 1); the trifluoroacetylation of **8** then gives ketone **9**. Obviously, the formation of compound **10** looks especially intriguing. Since the CF_3 should be a poor leaving group, we assumed that its elimination occurs as a two-step process involving *ipso*-substitution of CF_3 by $COCF_3$ group with the following protodetrifluoroacetylation. To test this hypothesis we subjected compound **8** to the action of TFAA in Et_2O (Scheme 2). Five ketones **9**, **11**–**14** were isolated in 48, 8, 6, 13, and 6% yields, respectively, along with 19% of the starting material (procedures S1, S2, Online Supplementary Materials). The formation of diketones **12** and **14** as well as monoketone **13** has clearly confirmed our assumption. Simultaneously, this experiment has demonstrated that the benzene ring carrying the NMe_2 group in **8** is activated towards electrophile much stronger than that fused with the pyrrole ring. The structures of all obtained benzo[*g*]indoles were supported by mass- and multinuclear (^{1}H, ^{13}C and ^{15}N) NMR spectra. Shortly, the most informative for the elucidation of benzo[*g*]indole structures was the disappearance in their ^{1}H NMR spectra of a signal of 1-NMe_2 group at δ 2.4–3.0 ppm instead of which a characteristic singlet of the pyrrole NMe group arose at δ 3.7–4.0 ppm. Compounds **10**, **13** and **14** with missed CF_3 group could be easily identified by the presence in their ^{1}H NMR spectra of two doublets at 6.6–7.2 ppm with the typical of pyrroles J_0 value of about 3 Hz.

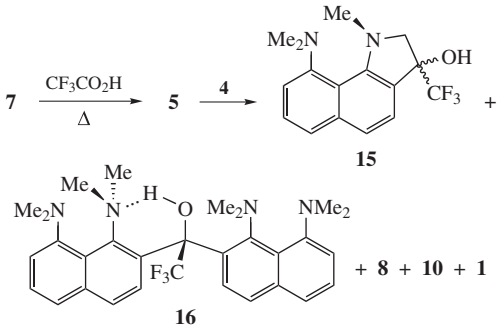


9 R^1 = H, R^2 = CF_3
11 R^1 = $C(O)CF_3$, R^2 = CF_3
12 R^1 = H, R^2 = $C(O)CF_3$
13 R^1 = R^2 = H
14 R^1 = $C(O)CF_3$, R^2 = H

Scheme 2

We also succeeded in rather effective preparation of monoketone **5** *via* protolytic deacetylation[8] (procedure S3) of more accessible diketone **7**. It was also found that treatment of ketone **5** with lithium derivative **4** gave benzo[*g*]indole alcohol **15** in 52% yield together with dinaphthylmethanol derivative **16** (28%) and trace amounts of indoles **8** and **10**; considerable quantity of DMAN **1** was also isolated as a result of protolysis of **4** (Scheme 3, procedure 2). Alcohol **15** is rather stable to dehydration, however, can be aromatized on treatment with SiO_2 or Al_2O_3 to afford compound **8** (procedure S4).‡

In case of 2,4-diketone **7**, the reaction with **4** proceeds in more complex fashion (Scheme 4). Here, 2-$COCF_3$ group is again engaged in the pyrrole cyclization (**17** → **18**) whereas its 4-$COCF_3$



Scheme 3

For **7**: orange crystals, yield 0.48 g (35%), mp 178–179 °C (lit.,[7] 180–182 °C); spectral properties are consistent with the authentic sample.

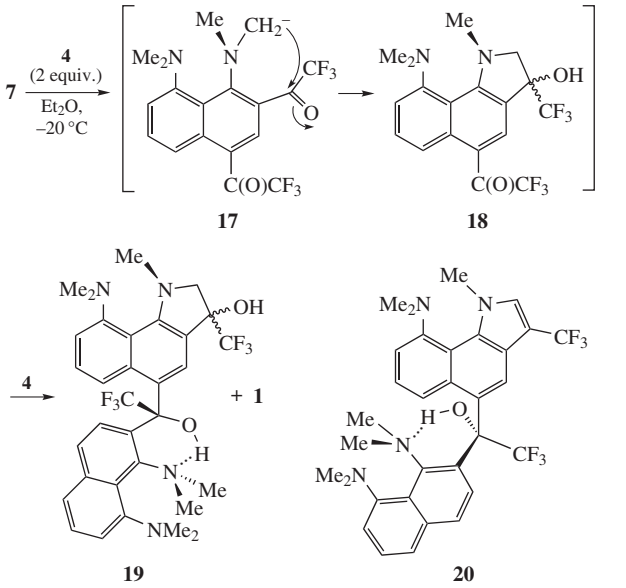
Procedure 2: reaction between **5** *and 2-lithio-1,8-bis(dimethylamino)-naphthalene* **4**. A solution of **5** (88 mg, 0.284 mmol) in dry Et_2O (6 ml) was added portionwise at –20 °C and under argon atmosphere to a solution of **4** in dry Et_2O (10 ml) obtained as indicated above from 2-bromo-1,8-bis(dimethylamino)naphthalene (166 mg, 0.568 mmol, 10 ml of Et_2O). A pale-orange reaction mixture was kept for 42 h at –20 °C and then treated with water (20 ml). The organic layer was separated and the aqueous one was extracted with Et_2O (5×5 ml). The combined organic extracts were evaporated to dryness and then subjected to column chromatography (37.6×1.7 cm) with Al_2O_3 (V), using light petroleum as an eluent. A yellowish fraction with R_f = 0.7 containing a mixture of compounds **8** and **10** (mixture 1) was collected. A subsequent elution was conducted with Et_2O–light petroleum mixture (1:2) to obtain sequentially the yellow and orange fractions. The former (mixture 2) contained 2,2′-binaphthyl alcohol **16** (R_f = 0.8) and proton sponge **1** while the latter (mixture 3) contained initial ketone **5** (R_f = 0.6) and indole alcohol **15** (R_f = 0.4). All three mixtures were evaporated to dryness. Mixture 1 (3 mg) was not separated; according to the ^{1}H NMR spectrum, it contained indoles **8** and **10** along with an unidentified component in a 4:2:1 proportion, respectively. Mixture 2 was chromatographed on a column (27×1.8 cm) with Al_2O_3 (V) using dichloromethane as an eluent. Colorless fractions of **16** (R_f = 0.4) and **1** (R_f = 0.1) were collected. Similar separation of mixture 3 with ethyl acetate–light petroleum (1:10) as an eluent gave ketone **5** (R_f = 0.7) and indole alcohol **15** (R_f = 0.5). After evaporation to dryness, the isolated compounds were obtained in the following total yields: **15**, 46 mg (52%); **16**, 42 mg (28%); **8**, 2 mg (2%); **10**, 1 mg (1%); **1**, 62 mg; **5**, 1 mg.

Procedure 3: reaction between **21** *and 2-lithio-1,8-bis(dimethylamino)-naphthalene* **4**. A solution of compound **21** (500 mg, 1.75 mmol) in dry Et_2O (9 ml) was added dropwise to a solution of **4** in dry Et_2O (25 ml) prepared as described above from 2-bromo-1,8-bis(dimethylamino)-naphthalene (1.024 g, 3.5 mmol) under argon atmosphere at –20 °C. The bright yellow mixture was kept at –20 °C for 72 h and then treated with water (30 ml). The organic layer was separated and the water layer was extracted with Et_2O (5×5 ml). The combined organic layers were evaporated to dryness and chromatographed by TLC (Al_2O_3, Et_2O–light petroleum, 1:1). Two fractions with R_f = 0.6 and 0.3 were collected. The first fraction (67 mg, 8%) represented ketone **22**, orange crystals, mp 171–172 °C (heptane). The second fraction (212 mg, 28%) contained practically pure indole **23**, beige crystals, mp 204–205 °C (decomp., MeCN).

If the reaction mixture was kept for 72 h at room temperature, ketone **22** became the major product (217 mg, 27%) and minor quantities of indole **23** (130 mg, 17%) were isolated.

For characteristics of compounds obtained, see Online Supplementary Materials.

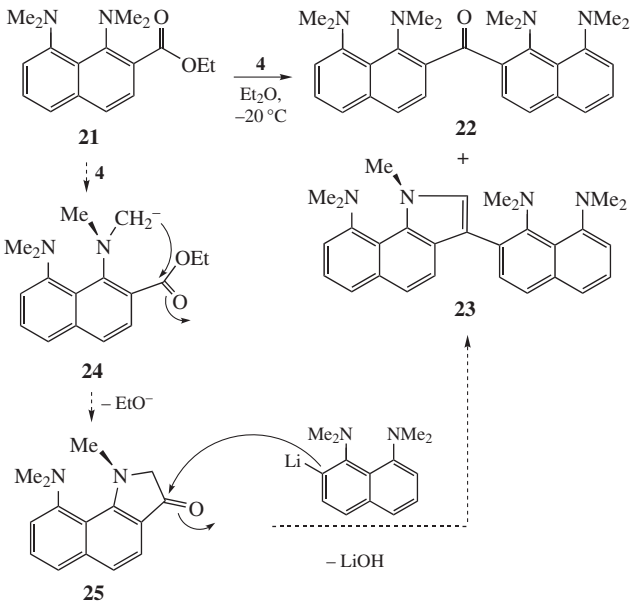
‡ Alcohol **16** demonstrates dynamic behavior, equilibrating between two equivalent hydrogen bonded structures. The switching process can be frozen at –60 to –55 °C against –90 °C for the analogue of **16** with the phenyl group instead of CF_3.[9]



Scheme 4

counterpart reacts with 2-lithio derivative **4** to produce dinaphthylmethanol **19** in 43% yield (procedure S5). It should be pointed out that alcohols of this type apparently constitute the main contents of the above mentioned red oligomer mixture. In particular, it is supported by the presence of several peaks between 12.6–12.8 ppm in the ^{1}H NMR spectrum of the latter, which are characteristic of the chelated tertiary hydroxyl group.[5] In addition, in one case we isolated from such a mixture small amount of crystals of compound **20**, whose structure was confirmed by X-ray diffraction study (Figure S3).

The reaction proceeded somewhat differently when lithium derivative **4** reacted with 2-ethoxycarbonyl one **21** (Scheme 5, procedure 3). We anticipated to obtain previously unknown ketone **22**. In fact, we isolated it along with benzo[*g*]indole derivative **23**, the ratio of the two products being strongly dependent on the reaction temperature. At 25 °C, compounds **22** and **23** were obtained in 27 and 17% yield, respectively, whereas at –20 °C they were formed in the reversed proportion: 8 and 28%. Since benzo[*g*]indole **23** cannot be obtained on treatment of authentic ketone **22** with **4**, we suggest that **23** is actually formed through the acidic ionization of the NMe group in ester **21**, followed by subsequent cyclization into pyrrolinone (**24** → **25**)



Scheme 5

and nucleophilic addition of **4** to the carbonyl group of **25**. The structure of **22** was proved by spectral data and X-ray diffraction (Figure S4).

To our knowledge,[10] such a pyrrole ring closure has not been reported previously. The combination of several factors can be responsible for this process in proton sponges: (1) the presence of rather strong *ortho*-electron-withdrawing group which acidifies the 1-NMe_2 group; for example, we have found that 2-benzoyl-1,8-bis(dimethylamino)naphthalene does not react similarly, (2) the exceptionally high proton affinity of naphthyllithium **4**, (3) the enhanced nucleophilicity of the aminomethyl anion of type **6**, (4) the assistance of lithium cation to the nucleophilic addition through its coordination with the carbonyl oxygen atom; the larger preference of the O→Li coordination over N→Li in aminomethyl anion **6** was evidenced by the results of DFT calculations (see Online Supplementary Materials), and (5) the favorable orientation of the ionized NMe and carbonyl groups. The importance of stereochemical factor is confirmed by X-ray study of ketones **5** and **7** (Figure S2). As seen, the anion moiety NCH_2^- should attack the appropriate carbonyl group having the most optimal orientation. The fact that the distance between the carbonyl carbon atom and the 1-NMe group in monoketone **5** (2.91 Å) is shorter than that in diketone **7** (2.96 Å)[11] can explain why **5** is cyclized easier than **7**.

To improve the yields of benzo[*g*]indoles as rather potent biologically active compounds and to spread the scope of the above reactions to other substrates, further studies are now in progress.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.007.

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