Journal of Organometallic Chemistry 855 (2018) 18–25

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Laying the way to *meta*-functionalization of naphthalene proton sponge via the use of Schlosser's superbase

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ARTICLE INFO

Article history:
Received 12 October 2017
Received in revised form
5 December 2017
Accepted 7 December 2017
Available online 12 December 2017

Keywords:
Proton sponge
Meta-functionalization
Organolithium
Metallation

ABSTRACT

Lithiation of 1,8-bis(dimethylamino)naphthalene (DMAN) with Schlosser's superbase (n-BuLi–t-BuOK) in the presence of TMEDA in hexane was examined. It has been shown that, compared with previously studied *n*-BuLi–TMEDA or *t*-BuLi–TMEDA mixtures, this reagent provides much more selective *meta*-lithiation. A variety of 3-substituted and 3,6-disubstituted derivatives of DMAN has been prepared in a good to reasonable yield after quenching the reaction mass with different electrophiles. A possibility of further functionalization of thus introduced *meta*-substituents to synthesize more complex 3-substituted derivatives of DMAN is also demonstrated.

1. Introduction

Direct *meta*-functionalization of arenes containing strong electron donating groups is still a challenge for modern organic chemistry due to the fact that their reactions with electrophiles yield mostly *ortho*- and *para*-substituted products [1]. Metal promoted processes gradually become a way to solve this problem. A number of copper [2], palladium [3] and zirconium [4] catalyzed meta-C–H functionalization reactions were suggested in the last decade, but all of them require a specific substrate with assisting groups. Metallation itself normally cannot be used for *meta*-derivatization of such compounds due to the DOM-effect [5] which favors the entry of metal into the *ortho*-position. Thus, on treatment of *N,N*-dimethylaniline (DMA) with *n*-butyllithium in Et_2O in the presence of *N,N,N,N*-tetramethylethylenediamine (TMEDA) only 2-lithium-*N,N*-dimethylaniline is formed in a good yield [6].

The situation considerably changes for naphthalene analogues of DMA due to the emergence of *peri*-interactions (review [7]). The latter often stabilize the transition state, leading to the formation of an 8-lithio derivative, e.g. **1a**→**2**, while a similar stabilization for *ortho*-metallation (**1b**→**3**) is less effective (Scheme 1) [8]. At the same time, the intrinsic acidity of ring CH-bonds can outweigh the *peri*-stabilization factor in some cases. For example, 1-methoxynaphthalene is preferably metallated by *n*-BuLi at position 2 owing to the stronger acidifying ability of oxygen in comparison with nitrogen atom in **1** [9].

The present work is devoted to the metallation of 1,8-bis(dimethylamino)naphthalene (DMAN, **4**) in attempt to elaborate a convenient method of its *meta*-functionalization. The matter is that reactions of DMAN with various electrophiles occur exclusively at the positions 2(7) and 4(5) and unavailability of its 3(6)-substituted derivatives for a long time represents an unfortunate gap in this area. Meanwhile, since the late 1960s, DMAN (trade mark "proton sponge") attracts a great interest as an aryl amine with abnormally high basicity [10] and exciting chemistry, useful organic reagent, platform for design of practically important compounds and convenient model for studying short strong hydrogen bonds and proton transfer in enzymic catalysis (reviews [11,12]). Unlike our recent work in which *n*-butyllithium and *tert*-butyllithium were employed for metallation of DMAN with rather modest results [13], we now report a much more encouraging use of a mixture of *t*-BuOK with *n*-BuLi. Earlier, this reagent, also known as LICKOR or Schlosser's superbase, was recommended for selective ionization of low acidic CH bonds [14].

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https://doi.org/10.1016/j.jorganchem.2017.12.007
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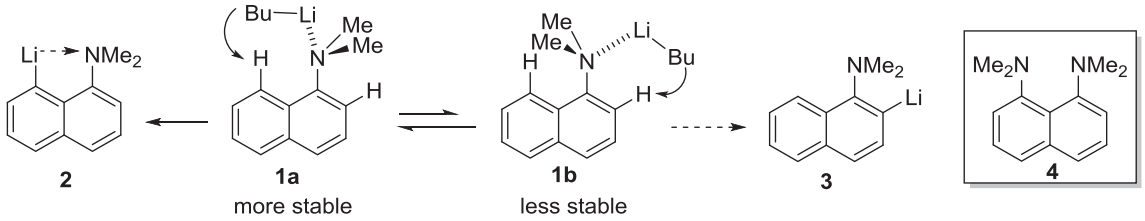


Scheme 1.

2. Experimental section

2.1. Material and measurements

Commercial hexane was distillated over sodium and benzophenone. Potassium *tert*-butoxide was prepared from commercially available *tert*-butyl alcohol and potassium on the day of each metallation experiment [15]. Commercial TMEDA was distillated over KOH just before each metallation experiment. Liquid-state NMR experiments were performed at 250 MHz for ^{1}H, 63 MHz for ^{13}C (Scientific and Educational Laboratory of Resonance Spectroscopy, Department of Natural and High Molecular Compounds Chemistry of Southern Federal University) and 500 MHz for ^{1}H and 126 MHz for ^{13}C (Centre for Magnetic Resonance, St. Petersburg State University). Chemical shifts are referred to TMS for ^{1}H and ^{13}C. The HR-ESI mass-spectra were obtained on a BRUKER maXis spectrometer equipped with an electrospray ionization (ESI) source; methanol was used as the solvent (Chemical Analysis and Materials Research Centre, St. Petersburg State University). The instrument was operated in positive mode using an m/z range of 50–1200. The capillary voltage of the ion source was set at 4000 V. The nebulizer gas pressure was 1.0 bar, and the drying gas flow was set to 4.0 L/min. Melting points were determined in glass capillaries on a Stuart SMP30 device and are uncorrected.

2.2. Metallation of **4**

1,8-bis(dimethylamino)naphthalene (200 mg, 0.9 mmol) and freshly prepared potassium *tert*-butoxide (418 mg, 3.7 mmol) were placed in a flame-dried, round-bottomed flask. 25 mL of freshly distillated over sodium *n*-hexane was added. The flask was filled with dry argon and closed with a serum cap. The mixture was cooled to −20 °C for 30 min, then freshly distillated TMEDA (0.6 mL, 3.7 mmol) and 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.7 mmol) were added. The greyish reaction mixture was stirred at −20 °C for 72 h. The resulting brown suspension (**A**) contains about 75% of 3-lithio-1,8-bis(dimethylamino)naphthalene **5a**.

2.2.1. 3-Formyl-, 4-formyl-, 3,5-diformyl- and 3,6-diformyl-1,8-bis(dimethylamino)naphthalenes (**6a-d**)

The absolute *N,N*-dimethylformamide (0.3 mL, 3.7 mmol) was added via syringe to the suspension **A**. The reaction mass was additionally stirred for 12 h at −20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on aluminium oxide with an EtOAc–*n*-hexane 1: 50 mixture as the eluent. Yellow fractions with $R_f = 0.6$ (**6a**), 0.3 (**6b**), 0.2 (**6d**) and 0.1 (**6c**) were collected.

3-Formyl-1,8-bis(dimethylamino)naphthalene (**6a**): yellow-orange oil; yield: 124 mg (55%). Characterization data were consistent with those reported in the literature [13].

4-Formyl-1,8-bis(dimethylamino)naphthalene (**6b**): dark-orange oil; yield: 16 mg (7%). Characterization data were consistent with those reported in the literature [16].

3,5-Diformyl-1,8-bis(dimethylamino)naphthalene (**6c**): orange crystals; mp 106–107 °C (*n*-hexane); yield: 3 mg (1%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 10.14 (s, 1H), 10.07 (s, 1H), 9.43 (d, $J = 1.0$ Hz, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 7.38 (d, $J = 1.0$ Hz, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 2.99 (s, 6H), 2.82 (s, 6H). ^{13}C NMR (126 MHz, δ, $CDCl_3$): 193.88, 191.37, 156.33, 151.92, 139.96, 136.50, 135.64, 124.88, 123.15, 119.90, 110.87, 107.29, 43.23. IR (KBr), ν_{max}/cm^{-1} 1645, 1686 (C=O). HRMS (ESI): found 271.1449 [M+H$^+$], 303.1712 [M+MeOH+H$^+$], 335.1976 [M+2MeOH+H$^+$]; calculated for $C_{16}H_{19}N_2O_2$[M+H$^+$] 271.1441, $C_{17}H_{23}N_2O_2$ [M+MeOH+H$^+$] 303.1703, $C_{18}H_{27}N_2O_2$ [M+2MeOH+H$^+$] 335.1965.

3,6-Diformyl-1,8-bis(dimethylamino)naphthalene (**6d**): orange crystals; mp 127–128 °C (n-hexane); yield: 8 mg (3%).^{1}H NMR (500 MHz, δ, $CDCl_3$): 10.08 (s, 2H), 7.92 (d, $J = 0.7$ Hz, 2H), 7.46 (d, $J = 0.7$ Hz, 2H), 2.84 (s, 12H). ^{13}C NMR (126 MHz, δ, $CDCl_3$): 192.38, 152.02, 136.78, 134.84, 128.82, 126.05, 110.53, 43.93. IR (KBr), ν_{max}/cm^{-1} 1690 (C=O). HRMS (ESI): found 271.1451 [M+H$^+$], 303.1716 [M+MeOH+H$^+$], 335.1980 [M+2MeOH+H$^+$]; calculated for $C_{16}H_{19}N_2O_2$[M+H$^+$] 271.1441, $C_{17}H_{23}N_2O_2$ [M+MeOH+H$^+$] 303.1703, $C_{18}H_{27}N_2O_2$ [M+2MeOH+H$^+$] 335.1965.

2.2.2. 3-Methylthio-1,8-bis(dimethylamino)naphthalenes (**7**)

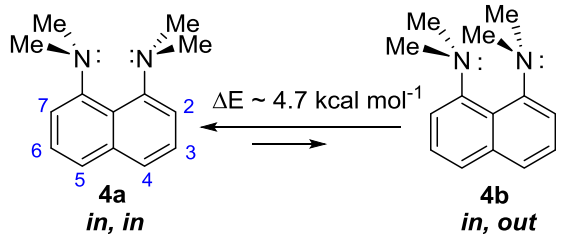
Absolute dimethyldisulfide (0.4 mL, 4.0 mmol) was added via syringe to the suspension **A**. The reaction mass was stirred additionally for 12 h at −20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on aluminium oxide with an EtOAc–*n*-hexane 1: 20 mixture as the eluent. Yellow fraction (almost colourless on adsorbent) with $R_f = 0.6$ was collected.

3-Methylthio-1,8-bis(dimethylamino)naphthalene (**7**): pale yellow oil with a weak “sulfide” odour; yield 116 mg (48%). Characterization data were consistent with those reported in the literature [13].

2.2.3. 3-Bromo-1,8-bis(dimethylamino)naphthalene (**8**)

Bromine (0.2 mL, 3.7 mmol) was added via syringe to the suspension **A**. The reaction mass was additionally stirred for 12 h at −20 °C and treated with water (10 mL). The products were extracted with hexane (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on aluminium oxide with *n*-hexane as the eluent. Pale yellow fraction with $R_f = 0.9$ was collected.

3-Bromo-1,8-bis(dimethylamino)naphthalene (**8**): pale yellow oil; yield: 57 mg (21%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 7.49 (d, $J = 1.8$ Hz, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 1.8$ Hz, 1H), 6.92 (d, $J = 7.1$ Hz, 1H), 2.80 (s, 6H), 2.79 (s, 6H). ^{13}C NMR (126 MHz, δ, $CDCl_3$): 152.19, 151.15, 138.72, 126.67, 123.33, 120.71, 119.71, 119.07, 116.02, 113.13, 44.36, 44.33. HRMS (ESI): 293.0662 (^{79}Br); calculated for $C_{14}H_{17}BrN_2$ (^{79}Br) 293.0648.



Scheme 2.

*2.2.4. 3-Trifluoroacetyl-1,8-bis(dimethylamino)naphthalene (**9**)*

Freshly distillated ethyl trifluoroacetate (0.4 mL, 3.7 mmol) was added via syringe to the suspension **A**. The reaction mass was additionally stirred for 12 h at −20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on aluminium oxide with an EtOAc–*n*-hexane 1: 30 mixture as the eluent. Yellow fraction with $R_f = 0.3$ was collected.

3-Trifluoroacetyl-1,8-bis(dimethylamino)naphthalene (**9**): dark orange oil; yield: 96 mg (33%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 8.09 (s, 1H), 7.49 (d, $J = 7.8$ Hz, 1H), 7.45–7.38 (m, 2H), 7.12 (d, $J = 7.8$ Hz, 1H), 2.85 (s, 6H), 2.82 (s, 6H). ^{13}C NMR (63 MHz, δ, $CDCl_3$): 180.93 (q, $J = 34.3$ Hz), 151.77, 150.90, 136.82, 127.11, 126.88 (dd, $J = 3.2$ Hz, $J = 6.5$ Hz), 124.12, 117.16 (q, $J = 291.6$ Hz), 116.75, 109.26, 44.21, 44.05. IR (liquid film), ν_{max}/cm^{-1} 1708 (C=O). HRMS (ESI): 331.1369 [M+H$^+$], 343.1632 [M+MeOH+H$^+$]; calculated for $C_{16}H_{18}F_3N_2O$ [M+H$^+$] 311.1366, $C_{17}H_{22}F_3N_2O$ [M+MeOH+H$^+$] 343.1628.

*2.2.5. 3-(2,2-Dimethylpropanonyl)- and 3,6-bis(2,2-dimethylpropanonyl)-1,8-bis(dimethylamino)naphthalenes (**10a,b**)*

Trimethylacetonitrile (0.4 mL, 3.7 mmol) was added via syringe to the suspension **A**. The reaction mass was additionally stirred for 12 h at −20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on aluminium oxide with an EtOAc–*n*-hexane 1: 30 mixture as the eluent. Yellow fractions with $R_f = 0.4$ (**10b**) and 0.6 (**10a**) were collected.

3-(2,2-dimethylpropanonyl)-1,8-bis(dimethylamino)naphthalene (**10a**): yellow waxy oil; yield: 67 mg (24%). ^{1}H NMR (500 MHz, δ, $CDCl_3$):7.77 (s, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 7.22 (s, 1H), 7.00 (d, $J = 7.4$ Hz, 1H), 2.82 (s, 6H), 2.81 (s, 6H), 1.43 (s, 9H)· ^{13}C NMR (126 MHz, δ, $CDCl_3$):209.33, 150.81, 150.78, 136.83, 134.98, 126.27, 122.83, 122.42, 121.73, 114.50, 111.55, 44.42, 44.34, 28.52. IR (liquid film), ν_{max}/cm^{-1} 1666 (C=O). HRMS (ESI): 299.2128 [M+H$^+$]; calculated for $C_{19}H_{26}N_2O$[M+H$^+$] 299.2118.

3,6-bis(2,2-dimethylpropanonyl)-1,8-bis(dimethylamino)naphthalenes (**10b**): yellow waxy oil; yield: 18 mg (5%). ^{1}H NMR (500 MHz, δ, $CDCl_3$):7.80 (s, 2H), 7.28 (s, 2H), 2.84 (s, 12H), 1.45 (s, 18H). ^{13}C NMR (126 MHz, δ, $CDCl_3$): 209.04, 150.54, 135.75, 135.70, 122.88, 122.48, 112.95, 44.39, 44.11, 28.30. HRMS (ESI): 383.2703 [M+H$^+$]; calculated for $C_{24}H_{35}N_2O_2$ [M+H$^+$] 383.2693.

*2.2.6. 3-Benzoyl-1,8-bis(dimethylamino)naphthalene (**11**)*

Benzoyl chloride (0.4 mL, 3.7 mmol) was added via syringe to the suspension **A**. The reaction mass was additionally stirred for 12 h at −20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on aluminium oxide with an EtOAc–*n*-hexane 1: 30 mixture as the eluent. Yellow fraction with 0.6 was collected.

3-Benzoyl-1,8-bis(dimethylamino)naphthalene (**11**): yellow oil; yield: 109 mg (37%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): ^{13}C NMR (126 MHz, δ, $CDCl_3$): 7.92–7.86 (m, 2H), 7.71 (d, $J = 1.3$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 2H), 7.43 (d, $J = 1.3$ Hz, 1H), 7.41–7.32 (m, 2H), 7.06 (dd, $J = 7.4$, 1.1 Hz, 1H), 2.86 (s, 6H), 2.84 (s, 6H). ^{13}C NMR (126 MHz, δ, $CDCl_3$): 197.12, 151.25, 150.77, 138.34, 136.66, 134.17, 132.07, 130.06, 128.20, 126.37, 126.17, 122.91, 122.33, 115.06, 111.43, 44.28, 44.22. HRMS (ESI): 319.1796 [M+H$^+$]; calculated for $C_{21}H_{22}N_2O$ [M+H$^+$] 319.1805.

*2.3. Functionalization of 3-formyl1,8-bis(dimethylamino) naphthalene **6a***

*2.3.1. 3-Formyl-1,8-bis(dimethylamino)naphthalene oxime (**12**)*

A solution of hydroxylamine hydrochloride (140 mg, 2 mmol) in 10 mL of ethanol was added to the solution of 3-formyl-1,8-bis(dimethylamino)naphthalene **6a** (280 mg, 0.9 mmol) in 50 mL of ethanol. The reaction mixture was stirred at room temperature for 24h. The solvent was removed in vacuum and the resulting white powder was mixed with 10 mL of aq. ammonia and 10 mL of chloroform. The organic layer was separated, and the water layer was extracted with chloroform Et_2O (2 × 10 mL). The combined organic fraction was dried over sodium sulphate. The solvent was removed, and the residue was chromatographed on aluminium oxide with an EtOAc–*n*-hexane 1:2 mixture as the eluent. Yellow fraction with $R_f = 0.5$ was collected.

3-Formyl-1,8-bis(dimethylamino)naphthalene oxime (**12**): yellow oil; yield: 190 mg (82%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 8.70 (s, 1H), 8.28 (s, 1H), 7.43 (s, 1H), 7.41–7.33 (m, 2H), 7.28 (d, $J = 0.9$ Hz, 1H), 7.01 (d, $J = 6.3$ Hz, 1H), 2.86 (s, 6H), 2.84 (s, 6H)· ^{13}C NMR (126 MHz, δ, $CDCl_3$): 151.38, 150.97, 150.92, 137.55, 129.06, 126.29, 123.22, 121.98, 121.37, 114.00, 108.27, 44.30, 44.20. HRMS (ESI): 258.1608 [M+H$^+$]; calculated for $C_{15}H_{20}N_3O$[M+H$^+$] 258.1601.

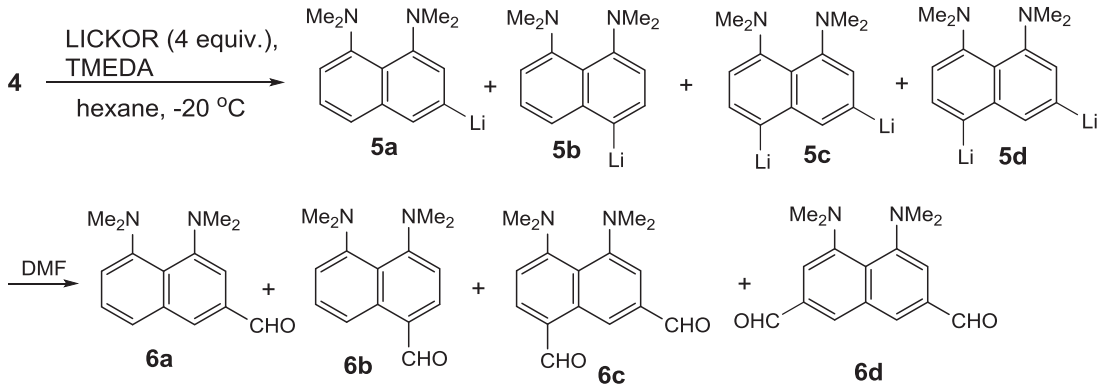
*2.3.2. 3-Cyano-1,8-bis(dimethylamino)naphthalene (**13**)*

A solution of 3-formyl-1,8-bis(dimethylamino)naphthalene oxime (200 mg, 0.8 mmol) in 10 mL of acetic anhydride was refluxed for 1h. The reaction mixture was poured on ice (50 g) and neutralized with aq. ammonia. The product was extracted with chloroform Et_2O (3 × 10 mL). The solvent was removed, and the residue was chromatographed on aluminium oxide with a CH_2Cl_2–*n*-hexane 2:1 mixture as the eluent. Yellow fraction with 0.9 was collected.

3-Cyano-1,8-bis(dimethylamino)naphthalene (**13**): yellow oil; yield: 170 mg (90%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 7.67 (d, $J = 1.1$ Hz,

Table 1
Results of control experiments on DMAN metallation with LICKOR after quenching the reaction mixture with DMF.

Run	RLi	TMEDA, equiv.	Time, h	Products yield (NMR), %					*Meta*/*para* selectivity
				1	6a	6b	6c	6d	
1	n-BuLi	0	24	48	32	11	4	5	3: 1
2	n-BuLi	4	24	42	48	6	1	3	8: 1
3	n-BuLi	4	48	35	51	6	3	5	7: 1
4	n-BuLi	4	72	11	76	9	1	3	8: 1
5	n-BuLi	4	96	12	75	8	2	3	9: 1
6	t-BuLi	4	24	78	16	5	1	0	3: 1



Scheme 3.

1H), 7.39 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 6.95 (d, $J = 1.1$ Hz, 1H), 2.82 (s, 6H), 2.79 (s, 6H). ^{13}C NMR (126 MHz, δ, $CDCl_3$): 151.51, 150.84, 136.85, 127.15, 126.81, 121.65, 121.60, 119.91, 115.38, 112.08, 108.80, 44.08, 43.95. IR (KBr), ν_{max}/cm^{-1} 2227 (CN). HRMS (ESI): 240.1501 [M+H$^+$]; calculated for $C_{15}H_{18}N_3$ [M+H$^+$] 240.1495.

2.3.3. *Ethyl 2-cyano-3-(1,8-bis(dimethylamino)naphthalen-3-yl) acrylate (**14**)*

Piperidine (0.04 mL, 0.4 mmol) and ethylcyanoacetate (0.04 mL, 0.4 mmol) were added to the solution of 3-formyl-1,8-bis(dimethylamino)naphthalene **6a** (100 mg, 0.4 mmol) in 10 mL of ethanol. The reaction mixture was stirred at room temperature for 24h. The solvent was removed in vacuum and the residue was chromatographed on aluminium oxide with a CH_2Cl_2–*n*-hexane 1:1 mixture as the eluent. Red fraction with $R_f = 0.5$ was collected.

Ethyl 2-cyano-3-(1,8-bis(dimethylamino)naphthalen-3-yl)acrylate (**14**): bloody red crystals; mp 107–108 °C (*n*-hexane); yield 70 mg (51%). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 8.31 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.41 (d, $J = 7.6$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.06 (d,

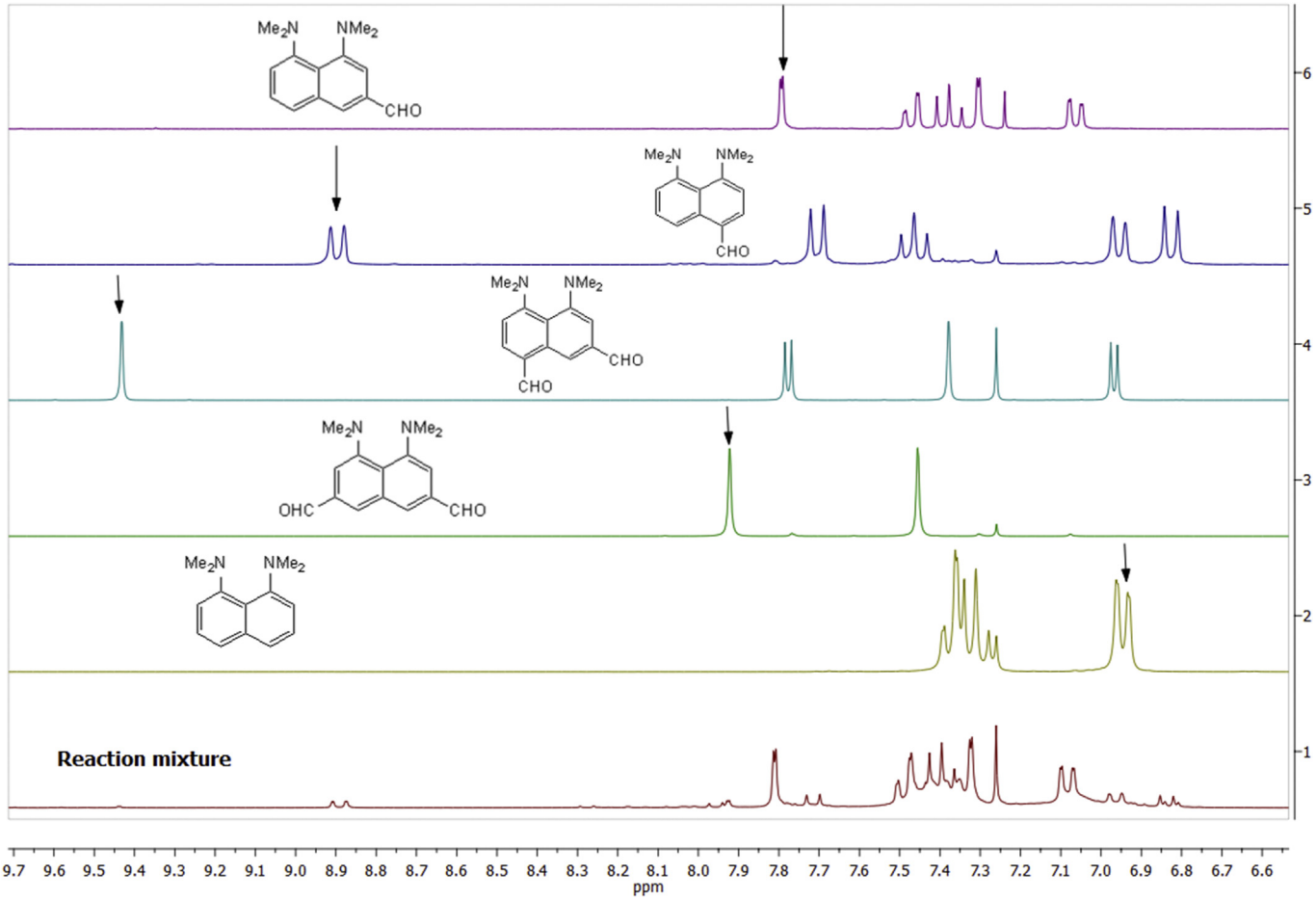


Fig. 1. ^{1}H NMR spectra of the reaction mixture for run 4 (Table 1) and authentic components (only aromatic area is shown; the indicator signals are marked by arrow).

$J = 7.3$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 1H), 2.86 (s, 6H), 2.82 (s, 6H), 1.42 (t, $J = 7.1$ Hz, 1H). ^{13}C NMR (126 MHz, δ, $CDCl_3$):163.09, 155.94, 151.55, 150.86, 137.08, 128.94, 128.85, 126.81, 122.78, 122.52, 116.10, 115.75, 110.18, 101.64, 62.52, 44.13, 44.03, 14.25. IR (KBr), ν_{max}/cm^{-1} 1726 (C═O), 2221 (CN). HRMS (ESI): 338.1867 [M+H$^+$]; calculated for $C_{20}H_{24}N_3O_2$ [M+H$^+$] 338.1863.

3. Results and discussion

At the beginning of this section, it is reasonable to briefly summarize our previous experiments on metallation of DMAN [13]. The use of *n*-BuLi and *tert*-BuLi for this aim has outlined the following internal factors which seem to be especially important: 1) strong electron-donor effect of two NMe_2 groups, 2) steric shielding of *ortho*-positions by NMe_2 groups, 3) the preference of *in/in* conformation of the NMe_2 groups **4a** over *in/out* form **4b** (Scheme 2) and 4) exceedingly high basicity (yet not estimated quantitatively) of 2-Li-DMAN. The first factor should promote the reduction of acidity of all ring C–H bonds but possibly to a lesser extent than that of *meta*-protons. This is the reason why in all metallation experiments, a considerable amount of DMAN is usually regenerated even after a prolonged incubation period. The factors 2–4 almost nullify the DOM-effect and hamper *ortho*-metallation [17-19]. These simple estimates allow us to understand why the ease of metallation of the ring C–H bonds in **4** changes in the sequence $C_{3(6)}$–H > $C_{4(5)}$–H ≫ $C_{2(7)}$–H. It is principally different from those in *N,N*-dimethylaniline and *N,N*-dimethyl(naphthyl-1)amine.

The aforementioned internal factors are closely interrelated with external ones, especially with a solvent used for metallation. The reaction very poorly proceeds in diethyl ether or tetrahydrofuran because of their participation in the protolysis of the formed lithium derivatives, in particular 2-Li-DMAN. Those satisfactory results can only be obtained in less acidic media such as hexane. Thus, a total yield of metallation products in hexane varies between 70 and 75%, whereas in diethyl ether it reaches 35% at best (with a fourfold excess of alkyllithium in the presence of TMEDA).

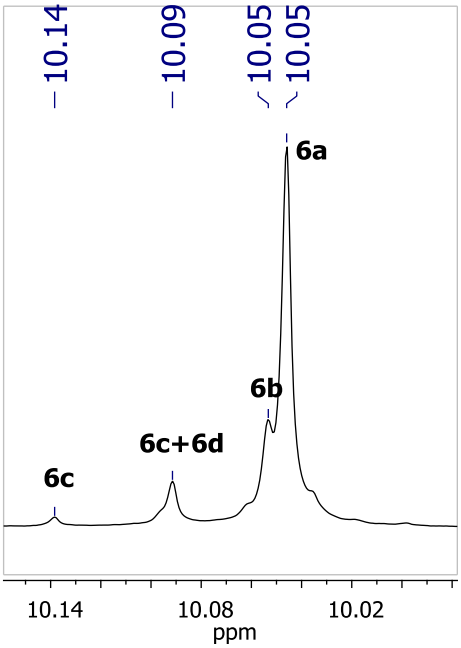
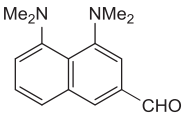
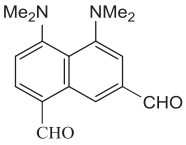
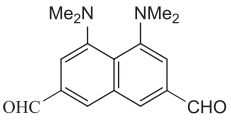
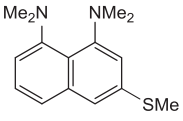
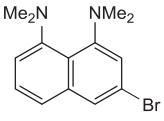
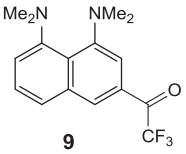
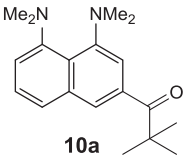
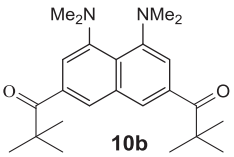
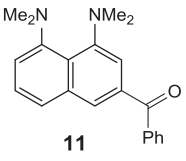
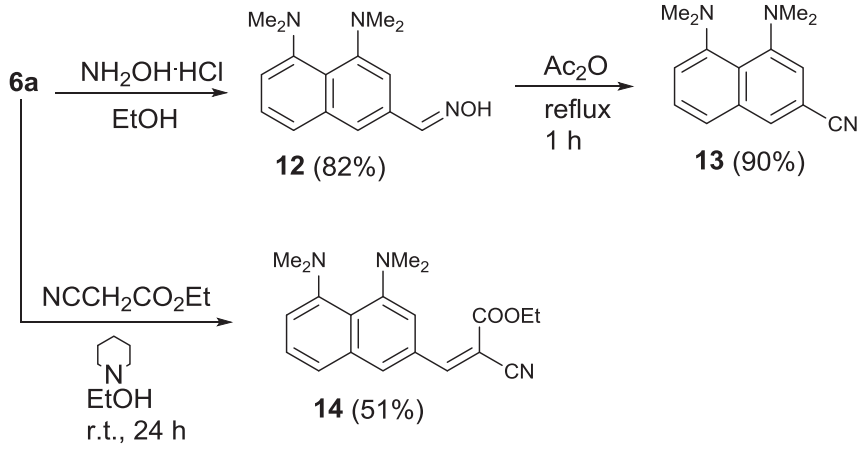


Fig. 2. Area of CHO groups in ^{1}H NMR spectrum for run 4 ($CDCl_3$, 250 MHz), signals of **6a**-**6d** are marked.

Table 2
Application of the developed DMAN lithiation protocol for the synthesis of its *meta*-derivatives.

Electrophilic reagent	Product	Yield (%)
DMF	 **6a**	55
	 **6c**	1
	 **6d**	3
MeSSMe	 **7**	48
Br_2	 **8**	21
CF_3COOEt	 **9**	33
t-BuCN	 **10a**	24
	 **10b**	5
PhCOCl	 **11**	37



Scheme 4.

Regrettably, by using both *n*-BuLi and *tert*-BuLi in hexane, 3- and 4-lithium derivatives of DMAN are obtained in nearly the same yields. This seriously weakens the preparative value of the method due to the difficult separation of target products after quenching the reaction mixture with an appropriate reagent. Until now, we were successful only in the isolation of pure 3-formyl- and 3-methylthio derivatives of DMAN in yields of about 32% each [13]. Here we present a much improved procedure for selective *meta*-metallation of DMAN, using a LICKOR reagent in conjunction with TMEDA [20,21]. We reasoned that the enhanced basicity and stronger steric demands of the reagent could discern a small difference in the acidity of C_3—H and C_4—H bonds. Our hopes were also reinforced by the fact that for *N,N*-dimethylaniline the D/H basic exchange is about two times faster for *meta*-position than for *para*-position [22,23].

First of all, we conducted a series of control experiments to optimize the reaction conditions for the DMAN metallation with LICKOR (Table 1). It was found that the reaction is best carried out at −20 °C in hexane using 4 M equivalents of a *t*-BuOK—*n*-BuLi—TMEDA mixture (runs 1,2). The process proceeds slowly; thus, prolonged stirring (run 2–4) with subsequent quenching of the crude reaction mass with DMF results in the formation of 3- and 4-monoaldehydes (**6a**, **6b**) and 4,5- and 3,5-dialdehydes (**6c**, **6d**) (Scheme 3). A 72-h metallation is considered to be optimal (run 4) and increasing the reaction time further did not significantly change these results (run 5). The attempt to increase the selectivity by using *t*-BuLi instead of *n*-BuLi failed: both total yield and *meta*-selectivity decreased (run 6). The compounds **6a-d,** along with unreacted DMAN, were first registered by ^{1}H NMR spectroscopy and then separated by TLC on alumina. The simplicity of the NMR spectra of previously unknown dialdehydes **6c,d** allowed an unambiguous assignment of their structure. The spectral yield of the aldehydes **6a-d** and indirectly their lithium predecessors **5a-d** was determined via intensities of aromatic proton signals characteristic for each compound (Fig. 1). The use of aldehyde proton signals was inconvenient due to their overlapping (Fig. 2).

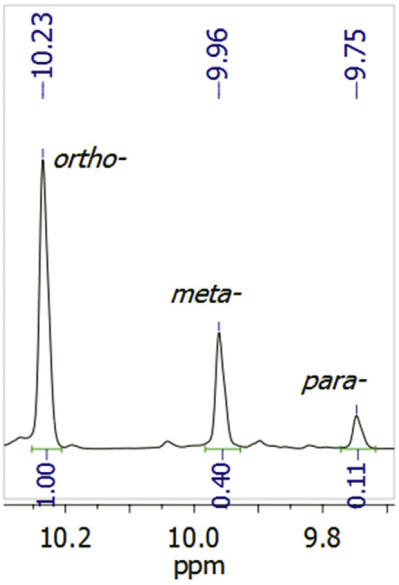
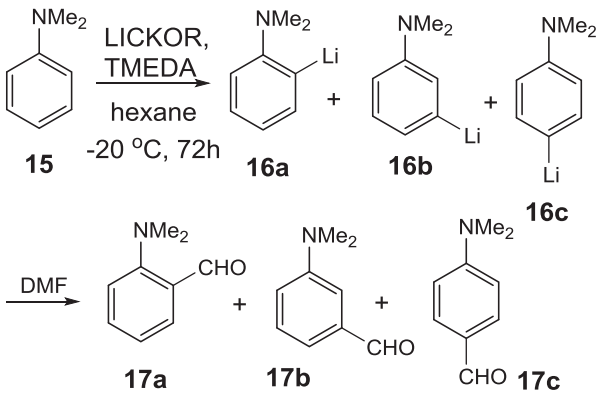


Fig. 3. Area of CHO groups in ^{1}H NMR spectrum ($CDCl_3$, 250 MHz) for the DMA metallation experiment.

To our satisfaction, no trace of *ortho*-metallation was fixed and the selectivity of *meta*-over *para*-metallation considerably increased to about 8: 1. The preparative yields of 3-aldehyde **6a** (55%) and 3-methylthio derivative **7** (48%) were also significantly higher as opposed to using *n*-BuLi or *t*-BuLi only. The optimized conditions were further used to synthesize other 3-substituted proton sponges, in particular 3-bromo-, 3-trifluoroacetyl, 3-benzoyl-DMAN (Table 2). There were no attempts to isolate minor products in these cases except for 3,6-dipivaloyl derivative **10b** [24,25]. The latter along with dialdehyde **6d** are the only 3,6-disubstituted derivatives of DMAN known to date. Their formation reflects the possibility of the ring dilithiation of DMAN with



Scheme 5.

LICKOR, which was also previously noted for naphthalene itself [26].

The method we have developed provides practically unlimited possibilities for obtaining other 3-substituted proton sponges through the functionalization of the *meta*-substituent. To illustrate this oxime **12**, cyanide **13**, and the product of Knoevenagel condensation with ethyl cyanoacetate **14** were prepared, starting from aldehyde **6a** (Scheme 4).

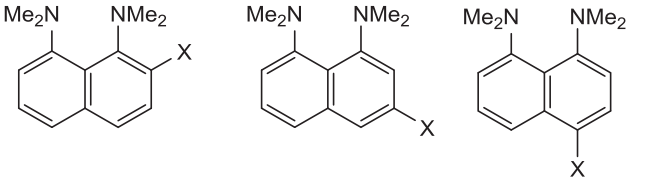
We also tested our metallation method on *N,N*-dimethylaniline (DMA, **15**). As it can be seen in Fig. 3, the reaction of DMA with the LICKOR-TMEDA mixture after quenching with DMF leads to the formation of *ortho*-, *meta*- and *para*-aldehydes **17a-c** (Scheme 5) with a relative yield of 10: 4: 1, respectively, which nicely correlates with the relative acidities of the ring CH bonds [22].

The availability of *meta*-substituted proton sponges made it possible to compare some of their physical properties with those of their *ortho*- and *para*-isomers. Most clearly, corresponding differences are manifested for carbonyl derivatives due to the absence of direct conjugation between the carbonyl and *peri*-NMe_2 groups in 3-aldehydes and ketones. Due to this, for example, the frequency of stretching vibrations, $\nu_{C=O}$, in IR spectra of 3-trifluoroacetyl-1,8-bis (dimethylamino) naphthalene, equal to 1708 cm^{-1}, is noticeably higher in comparison with its 2- (1616 cm^{-1}) [27] and 4-isomers (1660 cm^{-1}) [28]. Obviously, for the same reason, the difference in ^1H and ^{13}C chemical shifts, $\Delta\delta$, for 1- and 8-NMe_2 groups for *meta*-substituted derivatives is much less than compared with their 2- and 4-counterparts (Table 3).

4. Conclusions

It has been proven, that the preferable *in/in* conformation of NMe_2 groups provides the unique DMAN behavior towards metallation. First, it prevents the realization of the DOM-effect upon treatment with the *n*-BuLi–TMEDA mixture. Secondly, it sterically hinders the C2(7)–H bond from deprotonation by bulky LICKOR. This hampering of *ortho*-lithiation allowed us to develop an effective technique for the *meta*-derivatization of 1,8-bis(dimethylamino)naphthalene, based on the selective metallation of DMAN in position 3(6) with a LICKOR-TMEDA reagent. The method opened a way for the preparation of a wide range of 3-substituted and in some cases 3,6-disubstituted derivatives of DMAN, either via quenching the lithium intermediates with appropriate electrophiles or by the further functionalization of an already introduced 3-substituent.

Table 3
Comparison of chemical shifts for 1- and 8-NMe_2 groups in ^1H and ^{13}C NMR spectra ($CDCl_3$) of some *ortho*-, *meta*- and *para*-1,8-bis(dimethylamino)naphthalenes.



18 (X = CHO)
19 (X = $COCF_3$)
20 (X = Br)

6a (X = CHO)
9 (X = $COCF_3$)
8 (X = Br)

6b (X = CHO)
21 (X = $COCF_3$)
22 (X = Br)

Compound	δ (^1H), ppm			δ (^{13}C), ppm			Ref.
	1-NMe_2	8-NMe_2	Δδ	1-NMe_2	8-NMe_2	Δδ	
4 (X = H)	2.93	2.93	0	44.8	44.8	0	[29]
18	3.25	2.80	0.45	-[a]	-[a]	-[a]	[19]
6a	2.81	2.79	0.02	44.6	44.5	0.1	[13]
6b	2.96	2.77	0.19	43.2	43.3	0.1	[16,30]
19	3.13	2.73	0.40	46.0	43.6	2.4	[27]
9	2.85	2.82	0.03	44.2	44.1	0.1	[b]
21	2.90[c]	2.68[c]	0.22	-[a]	-[a]	-[a]	[28]
20	3.00	2.75	0.25	45.7	43.4	2.3	[31]
8	2.80	2.79	0.01	44.4	44.3	0.1	[b]
22	2.76	2.74	0.02	43.9	43.8	0.1	[32]

[a] No data available.
[b] This work.
[c] In CCl_4.

Acknowledgments

This work was supported by the Russian Foundation for Basic Research (project 16-33-60030).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jorganchem.2017.12.007.

References

[1] V.R. Taylor, Electrophilic Aromatic Substitution, Wiley, Chichester, 1990.
[2] a) R.J. Phipps, M.J. Gaunt, A *meta*-selective copper-catalyzed C–H bond arylation, Science 323 (2009) 1593–1597, https://doi.org/10.1126/science.1169975;
b) Y. Zhou, J. Zhao, L. Liu, *Meta*-selective transition-metal catalyzed arene C-H bond functionalization, Angew. Chem. Int. Ed. 48 (2009) 7126–7128, https://doi.org/10.1002/anie.200902762;
c) H.A. Duong, R.E. Gilligan, M.L. Cooke, R.J. Phipps, M.J. Gaunt, Copper(II)-Catalyzed *meta*-selective direct arylation of α-aryl carbonyl compounds, Angew. Chem. Int. Ed. 50 (2011) 463–466, https://doi.org/10.1002/anie.201004704.
[3] A. Dey, S. Agasti, D. Maiti, Palladium catalysed *meta*-C–H functionalization reactions, Org. Biomol. Chem. 14 (2016) 5440–5453, https://doi.org/10.1039/C6OB00395H.
[4] S. Akai, A.J. Peat, S.L. Buchwald, Regioselective, directed *meta* acylation of aromatic compounds, J. Am. Chem. Soc. 120 (1998) 9119–9125, https://doi.org/10.1021/ja981508t.
[5] V. Snieckus, Directed ortho-metalation. Tertiary amide and O-carbamate directors in synthetic strategies for polysubstituted aromatics, Chem. Rev. 90 (1990) 879–933, https://doi.org/10.1021/cr00104a001.
[6] a) H.T. Al-Masri, J. Seizer, P. Lönnecke, S. Blaurock, K. Domasevitch, E. Hey-Hawkins, Synthesis and molecular structures of (2-dialkylaminophenyl)alcohols and of 2-phenylaminoalkyl-dimethylaminobenzene derivatives, Tetrahedron 60 (2004) 333–339, https://doi.org/10.1016/j.tet.2003.11.022;
b) A.R. Lepley, W.A. Khan, A.B. Giumanini, A. G Giumanini, Metallation of *N,N*-Dimethylaniline, J. Org. Chem. 31 (1966) 2047–2051, https://doi.org/10.1021/jo01345a001.
[7] A.F. Pozharskii, O.V. Ryabtsova, Organolithium and organomagnesium compounds of the naphthalene series in organic synthesis, Russ. Chem. Rev. 75 (2006) 709–736, https://doi.org/10.1070/RC2006v075n08ABEH003611.
[8] D.R.W. Hodgson, A.J. Kirby, N. Feeder, The case of the missing acetylene. The mechanism of an intramolecular $S_N(V)$ reaction and a new route to 1-methylbenzo[*de*]quinolones, J. Chem. Soc., Perkin Trans. 1 (1999) 949–954, https://doi.org/10.1039/A900090I.
[9] J. Betz, W. Bauer, NMR and calculational studies on the regioselective lithiation of 1-methoxynaphthalene, J. Am. Chem. Soc. 124 (2002) 8699–8706, https://doi.org/10.1021/ja010456w.
[10] R.W. Alder, P.S. Bowman, W.R.S. Steele, D.R. Winterman, The remarkable basicity of 1,8-bis(dimethylamino)naphthalene, J. Chem. Soc., Chem. Commun (1968) 723–724, https://doi.org/10.1039/C19680000723.
[11] A.F. Pozharskii, V.A. Ozeryanskii, Proton sponges, in: Z. Rappoport (Ed.), The Chemistry of Anilines, J. Wiley & Sons, Chichester, 2007, p. 931. Part 2, Chapter 17.
[12] A.F. Pozharskii, V.A. Ozeryanskii, Proton sponges and hydrogen transfer phenomena, Mendeleev Commun. 22 (2012) 117–124, https://doi.org/10.1016/j.mencom.2012.05.001.
[13] A.S. Antonov, A.F. Pozharskii, V.A. Ozeryanskii, A. Filarowski, K.Y. Suponitsky, P.M. Tolstoy, M.A. Vovk, Ring lithiation of 1,8-bis(dimethylamino)naphthalene: another side of the 'proton sponge coin', Dalton Trans. 44 (2015) 17756–17766, https://doi.org/10.1039/c5dt02482j.
[14] a) M. Schlosser, J.H. Choi, S. Takagishi, Selective mono- or dimetalation of arenes by means of superbasic reagents, Tetrahedron 46 (1990) 5633–5648, https://doi.org/10.1016/S0040-4020(01)87763-2;
b) M. Schlosser, The 2×3 toolbox of organometallic methods for regiochemically exhaustive functionalization, Angew. Chem. Int. Ed. 44 (2005)

376–393, https://doi.org/10.1002/anie.200300645.
[15] W.S. Johnson, W.P. Schneider, β-carbethoxy-γ,γ-diphenylvinylacetic acid, Org. Synth. 30 (1950) 18, https://doi.org/10.15227/orgsyn.030.0018.
[16] N.V. Vistorobskii, A.F. Pozharskii, Peri-naphthylenediamines VII. Aldehydes of "proton sponge", Zh. Org. Khim. 25 (1989) 2154–2161. Chem. Abstr. 112 (1990) 234930m.
[17] The preference of *in/in* conformation is determined by steric repulsion of four bulky methyl groups. In accordance with theoretical calculations [18] the energy difference between *in/in* and *in/out* forms in the gas phase is equal to 4.7 kcal mole^{-1}. Nevertheless, the *in/out* form becomes more advantageous in some ortho-substitutedprotonsponges. [19] It is difficult to say how this circumstance can affect the activation energy of *ortho*-metallation, especially since some amount of the 2-lithium derivative is yet formed at the beginning of the reaction as a kinetic product that is isomerized further into a mixture of 3- and 4-lithium derivatives. The instability of 2-Li-DMAN is most likely the result of its particularly high basicity caused by the proximity of three unshared electron pairs on nitrogen atoms and the carbanion center.
[18] A. Szemik-Hojniak, J.M. Zwier, W.J. Buma, R. Bursi, J.H. van der Waals, Two ground state conformers of the proton sponge 1,8-bis(dimethylamino)naphthalene revealed by fluorescence spectroscopy and ab initio calculations, J. Am. Chem. Soc. 120 (1998) 4840–4844, https://doi.org/10.1021/ja974245w.
[19] A.F. Pozharskii, A.V. Degtyarev, O.V. Ryabtsova, V.A. Ozeryanskii, Z.A. Starikova, M.E. Kletzkii, L. Sobczyk, A. Filarowskii, 2-α-hydroxyalkyl- and 2,7-di(α-hydroxyalkyl)-1,8- bis(dimethylamino)naphthalenes: stabilization of nonconventional in/out conformers of "proton sponges" via n···H-O intramolecular hydrogen bonding. A remarkable kind of tandem nitrogen inversion, J. Org. Chem. 72 (2007) 3006–3019, https://doi.org/10.1021/jo062667v.
[20] TMEDA was added to LICKOR to increase reagent basicity and to improve *meta:para* ratio. This approach is used for lithiation of benzene under mild conditions [21].
[21] L. Brandsma, H.D. Verkruijsse, Preparative Polar Organometallic Chemistry, Volume 1, Chapter VI Metallated Aromatic Compounds, Springer-Verlag, Berlin, 1987.
[22] It should be noted that partial rate factors for D/H exchange of the ring hydrogen atoms in DMA (KNH_2, liq. NH_3, 25°C) range in the following order: 18.3 (*ortho*) : 2.1 (*meta*) : 1 (*para*) [23]. This sequence can be well explained by negative inductive effect of the nitrogen atom of the NMe_2 group especially since the K^+ is a poorly coordinating metal to participate in the DOM effect. Apparently, the role of the latter increases sharply in the case of organometallic reagents with well-coordinating ions, for example, Li^+.
[23] A.I. Shatenshtein, Y.I. Ranneva, Factors of the partial exchange rate of deuterium in dimethylaniline with a solution of potassium amide in liquid ammonia and the mechanism of the basic deuterium exchange, J. Gen. Chem. U. S. S. R. 31 (1961) 1317–1326.
[24] It is noticeable, that quenching of the reaction mixture after metallation with trimethylacetonitrile results in formation of ketones **10**, but not corresponding imines. The latter seems to be unstable to hydrolysis in contrast to *ortho*-ketimines of DMAN [25].
[25] A.S. Antonov, V.Y. Mikshiev, A.F. Pozharskii, V.A. Ozeryanskii, ortho-Ketimines of 1,8-Bis(dimethylamino)naphthalene: synthesis, hydrolytic stability and transfer of basicity from proton sponge moiety to the imino function, Synthesis 46 (2014) 3273–3282, https://doi.org/10.1055/s-0034-1379008.
[26] It has been shown that metallation of naphthalene with LICKOR yields the mixture of 1- and 2-monosubtitued and 1,2-, 1,3-, 1,4-, 1,5-, 2,3-, 2,5-,2,6-, 2,7- and 2,8-disubstituted products with 45:55 α : β-ratio [14a].
[27] S.G. Kachalkina, G.S. Borodkin, A.F. Pozharskii, A.S. Antonov, I.G. Borodkina, Y.F. Maltsev, E.A. Filatova, A. Filarowski, V.A. Ozeryanskii, Base-promoted transformation of 2-C(O)R-1,8-bis(dimethylamino)naphthalenes into benzo [g]indole derivatives, Mendeleev Commun. 25 (2015) 182–184, https://doi.org/10.1016/j.mencom.2015.05.007.
[28] N.V. Vistorobskii, A.F. Pozharskii, Peri-naphthylenediamines X. Acylation of "Proton Sponge". Approaches to phenalenons on it's base, Zh. Org. Khim 27 (1991) 1543–1552.
[29] M. Darabantu, T.L. equeux, J.-C. Pommelet, N. Ple, A. Turck, Selective fluorination by halogen exchange of chlorodiazines and chloropyridines promoted by the 'proton sponge'—triethylamine tris(hydrogen fluoride) system, Tetrahedron 57 (2001) 739–750, https://doi.org/10.1016/S0040-4020(00)01060-7.
[30] R. Nazir, B. Thorsted, E. Balčiūnas, L. Mazur, I. Deperasińska, M. Samoć, J. Brewer, M. Farsari, D.T. Gryko, π-Expanded 1,3-diketones – synthesis, optical properties and application in two-photon polymerization, J. Mater. Chem. C 4 (2016) 167–177, https://doi.org/10.1039/C5TC03334A.
[31] N.J. Farrer, R. McDonald, J. Scott McIndoe, Proton sponge phosphines: electrospray-active ligands, Dalton Trans. (2006) 4570–4579, https://doi.org/10.1039/b609561e.
[32] M. Pietrzak, L. Stefaniak, A.F. Pozharskii, V.A. Ozeryanskii, J. Nowicka-Scheibe, E. Grech, G.A. Webb, A ^{1}H, ^{13}C and ^{15}N NMR investigation of three substituted DMAN derivatives and their monoprotonated salts, J. Phys. Org. Chem. 13 (2000) 35–38, https://doi.org/10.1002/(SICI)1099-1395(200001)13:1<35::AID-POC202>3.0.CO;2-N.