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NOVEL FORMALDEHYDE-MEDIATED DIMERIZATION REACTION OF *N*-ALKYL-1-NAPHTHYLAMINE DERIVATIVES UNDER MILD/NEUTRAL CONDITIONS; APPLICATION TO SYNTHESIS OF NAPHTHYLAMINE-DERIVED MACROCYCLES

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Abstract - The dimerization reaction of *N*-methyl-1-naphthylamine (**1**) with formaldehyde is described. Reaction of **1** with formaldehyde under mild/neutral conditions gave bis-4-(1-*N*-methylaminonaphthyl)methane (**2**) in high yield as a single dimerization product. This formaldehyde-mediated aromatic condensation reaction is chemo- and regio-selective, and it takes place particularly with *N*-monoalkyl-1-naphthylamines as substrates. The novel naphthylamine-derived macrocyclic compounds 1,6,28,33-tetraaza-[6.1.6.1]paranaphthalenophane (**13a**) and 1,13-diaza[13,1]paranaphthalenophane (**12c**) were synthesized by application of this formaldehyde-mediated mild/neutral condensation reaction as the key step.

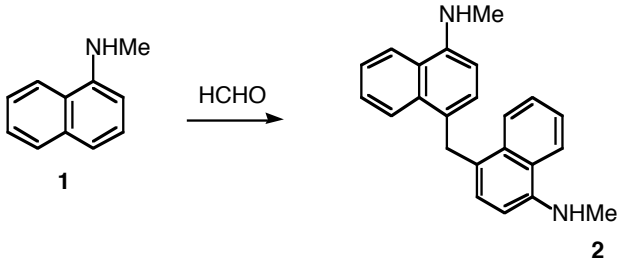
Many studies on formaldehyde (FA)-related reactions have been reported over the past few decades.[1-5] FA reacts with nucleophiles as a C1 unit to give a variety of useful functional groups in organic synthesis, e.g., in alkylation at carbonyl α-positions,[1] hydroxymethylation of aromatic rings,[2] addition to alkenes

(ene reaction),[3] condensation with alkenes in the presence of Brϕnsted acids (known as the Prins reaction),[4] and the Mannich reaction.[5]

On the other hand, FA is also well known as an embalming agent and as a genotoxic substance that causes DNA-protein or DNA-DNA cross-link formation.[6] In the course of our recent work on FA-mediated modification of nucleic acids with aromatic amines,[7] we found that the reaction of *N*-methyl-1-naphthylamine (**1**) with FA under neutral and very mild conditions gave bis-4-(1-*N*-methylaminonaphthyl)methane (**2**) in good yield as a single product. In general, in the presence of FA, *N*-methylaniline is known to be converted into iminal derivatives (R_1R_2N-CH_2-NR_1R_2: R_1=Ph, R_2=Me) *via* an imine intermediate,[8] or Friedel-Crafts type alkylation or condensation of aromatic compounds with aldehyde usually takes place under acidic or basic conditions.[2,9] Thus, FA-mediated reaction of *N*-methyl-1-naphthylamine (**1**) appears to be a novel chemo- and regio-selective alkylation under neutral conditions.

We were interested in this novel and facile FA-mediated C-C bond-forming reaction of naphthylamine derivatives.[10] In this paper, we describe the FA-mediated dimerization of naphthylamine derivatives and its application to macrocyclic compound syntheses.

Table 1. Formaldehyde-Mediated Dimerization of *N*-Methyl-1-naphthylamine[a]



1 **2**

Entry	Solvent	Temp	Time	Yield (%)[b]
i	MeOH	rt	5 h	84
ii	MeCN	rt	5 h	85
iii	THF	rt	48 h	20
iv	MeOH-5% AcOH	rt	1 h	90
v	5% HCl aq	rt	1 min	95

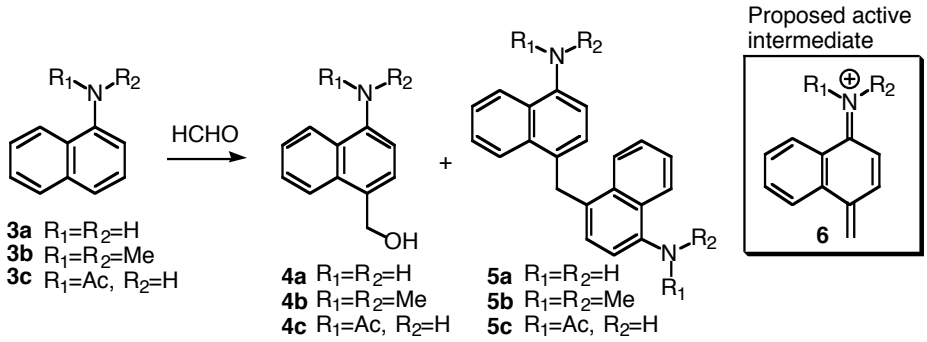
[a] 0.3 mol/L of **1** and 10 equiv. of 35% HCHO were used. [b] Isolated yield.

Reaction of **1** with FA in MeCN or MeOH under neutral conditions gave bis-4-(1-*N*-methylaminonaphthyl)methane (**2**) in high yield (Table 1. Entries i, ii). The structure of the adduct (**2**) was determined by NMR and MS spectroscopic analysis after acetylation of the amino group.[11] The dimerization reaction was suppressed in THF (Entry iii), but remarkably accelerated in acidic media. In aqueous hydrogen chloride solution, this reaction was completed within 1 min and gave **2** almost quantitatively (Entries iv, v) without forming Mannich-type reaction products of **1** *via* an iminium ion intermediate, which is usually observed under acidic reaction conditions. Thus, this FA-mediated dimerization of *N*-methyl-1-naphthylamine (**1**) appears to be chemo- and regio-specific under both neutral and acidic conditions.

To investigate the generality of this FA-mediated dimerization reaction with naphthalene derivatives having an electron-donating group at the C1-position, reactions of 1-substituted naphthalenes with FA were examined (Table 2). Treatment of 1-naphthylamine (**3a**) with an excess amount of FA gave a complex mixture of polymeric products (Entry i). *N,N'*-Dimethyl- and *N*-acetyl-1-naphthylamines (**3b**, **3c**), did not react with FA under neutral conditions even at higher temperature (Entries ii, v). On the other hand, when the reaction was performed in AcOH as a solvent, *N,N'*-dimethyl-1-naphthylamine (**3b**) gave the 4-hydroxymethylated product (**4b**) together with the dimer (**5b**) (Entries iii, iv).[12] Dimerization of *N*-acetyl-1-naphthylamine (**3c**) did not take place in AcOH solution (Entry. vi). Condensation of the 4-hydroxymethylated product (**4b**) with an equal amount of **3b** gave the corresponding dimer (**5b**) quantitatively, just upon heating in AcOH at 80°C.

Though this 4-hydroxylmethylnaphthylamine (**4**) is a possible intermediate in the FA-mediated condensation reaction, **4** could not be observed in the reaction of *N*-methyl-1-naphthylamine (**1**). These dimerization reactions of the 1-naphthylamine derivatives (**1**) and (**3b**) with FA may proceed *via* the putative reactive intermediate dienoiminium ion (**6**).

Table 2. Formaldehyde-Mediated Dimerization of 1-Naphthylamine Derivatives[a]



3a R_1=R_2=H
3b R_1=R_2=Me
3c R_1=Ac, R_2=H

4a R_1=R_2=H
4b R_1=R_2=Me
4c R_1=Ac, R_2=H

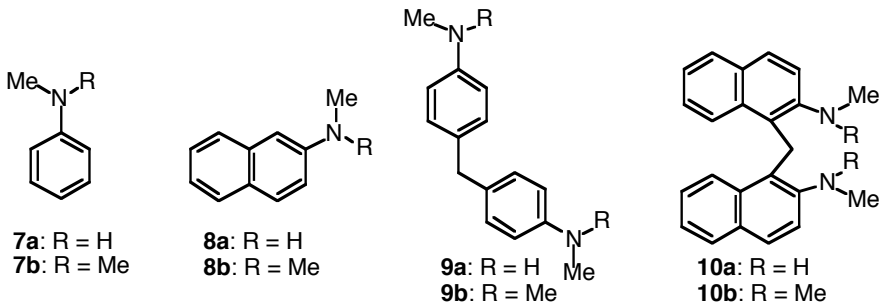
5a R_1=R_2=H
5b R_1=R_2=Me
5c R_1=Ac, R_2=H

Entry	R_1	R_2	Solvent	Temp	Time (h)	Yield (%)[b]	
						4	**5**
i	H	H	MeOH	rt	5	polymerized	
ii	Me	Me	MeOH	70°C	48	-	-
iii	Me	Me	AcOH	rt	48	17	19
iv	Me	Me	AcOH	70°C	2	15	50
v	Ac	H	MeOH	rt	48	-	-
vi	Ac	H	AcOH	70°C	3	-	-

[a] 0.3 mol/L of **3** and 10 equiv. of 35% HCHO were used. [b] Isolated yield.

FA-mediated dimerization reactions of other aromatic amines were examined (Figure 1). Alkylation of both *N*-methylaniline (**7a**) and *N*-methyl-2-naphthylamine (**8a**) with FA under neutral conditions selectively proceeded onto nitrogen and gave iminal derivatives.[13] Under acidic conditions (in AcOH), **7a** and **8a** were polymerized with FA. On the other hand, *N,N*-dimethylaniline (**7b**) and *N,N'*-dimethyl-2-naphthylamine (**8b**) gave the corresponding dimers (**9b**) and (**10b**) in AcOH as a solvent in 82 and 45% yields, respectively,[12,14] while this dimerization reaction of **7b** and **8b** did not proceed under neutral conditions.

Figure 1. Dimerized Aromatic Amines by Formaldehyde-Mediated Condensation



7a: R = H
7b: R = Me

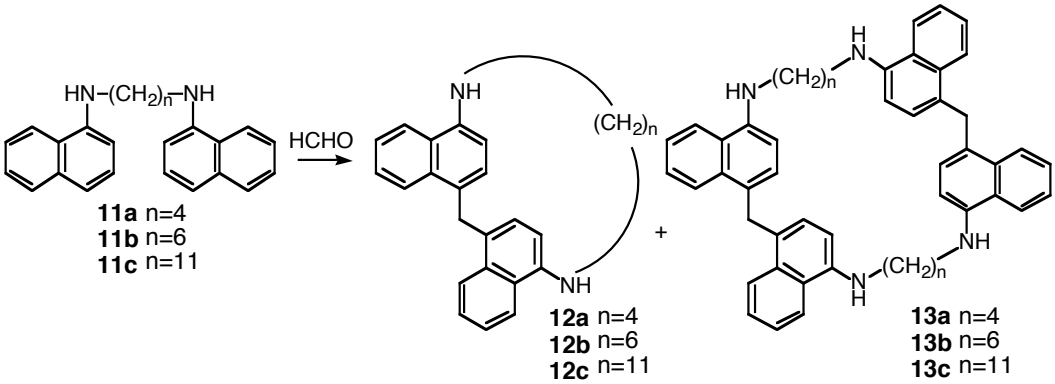
8a: R = H
8b: R = Me

9a: R = H
9b: R = Me

10a: R = H
10b: R = Me

We applied this specific condensation reaction of naphthylamine for construction of macrocyclic compounds. The FA-mediated direct alkylation and subsequent condensation of aromatic compounds are a useful synthetic method to create macrocyclic compounds such as calix[n]arene or porphyrin derivatives,[9] and the biarylaminomethane skeleton is a basic component of cyclophanes,[15] which are widely utilized as artificial organic hosts. Thus, we examined naphthylamine-type cyclophane (naphthalenophane)[16] synthesis by applying this condensation reaction to the *N*-alkyl-1-naphthylamine derivatives (**11a-c**),[15a] and the results are summarized in Table 3.

Table 3. Synthesis of Naphthalenophanes *via* the FA-mediated Condensation



Entry	n	Solvent	Concentration (mmol/L)	HCHO (eq)	Temp	Time (h)	Yield (%)[a]	
							12	**13**
i	4	MeOH	1	25	rt	17	-	27
ii	6	MeCN[b]	3	80	60°C	30	-	3[c]
iii	11	MeOH	1	80	60°C	48	45	-

[a] Isolated yield. [b] Compound (**11b**) was hardly desolved in MeOH. [c] Linear dimer of **11b** was obtained in 8% yield.

Reaction of **11a** with FA took place to give the cyclodimerized cyclophane (**13a**) in 27% yield (Entry i). Elongation of the methylene spacer from butyl to hexyl essentially blocked this cyclodimerization. Even at a higher concentration (3 mmol/L) and with an excess of FA, **11b** gave only a trace amount of the cyclophane (**13b**), while the linear dimer of **11b** was formed predominantly (Entry ii). This remarkable difference of reactivity in the cyclization step is presumably due to the different conformation and/or solubility of the linear precursor. Solubility of **11b** and the cyclodimerized product (**13b**) in MeOH or MeCN is very poor compared to that of **11a** and **13a**. In contrast to the cyclization of **11a** and **11b**, the

intramolecularly cyclized cyclophane (**12c**) was obtained in a good yield from **11c**, which has a further elongated spacer (Entry iii). This novel naphthylamine oligomer is a new variety of cyclophane, and this new cyclophane synthetic method has potential applications in the field of supramolecular chemistry.

In summary, we found selective C-C bond formation in the reaction of *N*-methyl-1-naphthylamine (**1**) with FA under very mild neutral conditions. This novel condensation reaction is classified as a substrate-specific aromatic substitution reaction for *N*-alkyl-1-naphthylamines, such as **1** or **11**. Moreover, we succeeded in applying this novel FA-mediated dimerization reaction to naphthylamine-derived cyclophane synthesis.

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EXPERIMENTAL

The general procedure of the reaction. To 1-naphthylamine derivatives (**1** or **3**) in appropriate solvents was added 35% formaldehyde solution (10 eq), and then the mixture was stirred with monitoring of the reaction. After the usual work up, the adduct (**2**, **4**, **5**) was purified by silica gel column chromatography.

***N,N'*-Dimethyl-4-hydroxymethyl-1-naphthylamine** (**4b**): Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.89 (6H, s), 5.06 (2H, s), 7.01 (1H, d, J = 7.5 Hz), 7.40 (1H, d, J = 7.5 Hz), 7.51 (1H, t, J = 7.5 Hz), 7.54 (1H, t, J = 7.5 Hz), 8.13 (1H, d, J = 7.5 Hz), 8.28 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 45.23, 63.80, 113.28, 124.25, 124.79, 125.19, 125.98, 126.26, 129.06, 130.91, 132.60, 151.26; HRFABMS. Calcd for $C_{25}H_{26}N_2$ (M^+): 354.2096. Found: 354.2115.

Bis-4-(1-*N*,*N*'-dimethylaminonaphthyl)methane (**5b**): Colorless solid, mp 103-105°C (hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.87 (12H, s), 4.75 (2H, s), 6.95 (2H, d, J = 7.6 Hz), 6.98 (2H, d, J = 7.6 Hz), 7.46 (2H, t, J = 7.5 Hz), 7.51 (2H, t, J = 7.5 Hz), 8.02 (2H, d, J = 8.0 Hz), 8.33(2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.23, 45.41, 113.93, 124.49, 124.68, 124.99, 125.90, 126.94, 129.00, 133.34; FABMS. 354 $(M)^+$. HRFABMS. Calcd for $C_{27}H_{27}N_2O_2$ (MH^+): 411.2073. Found: 411.2054.

Bis-4-(1-*N*,*N*'-dimethylaminoanilino)methane (**9b**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.89 (12H, s), 3.80 (2H, s), 6.88 (4H, d, J = 8.8 Hz), 7.05 (4H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.85, 40.93, 113.06, 129.38, 130.37, 149.02; HRFABMS. Calcd for $C_{17}H_{22}N_2$ (M^+): 254.1783. Found: 254.1883.

Bis-1-(2-*N*,*N*'-dimethylaminonaphthyl)methane (**10b**): Colorless solid, mp 100-103°C (hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.18 (12H, s), 5.14 (2H, s), 7.10 (2H, t, J = 7.5 Hz), 7.14 (2H, t, J = 7.2 Hz), 7.46 (2H, d, J = 8.9 Hz), 7.58 (2H, d, J = 8.0 Hz), 7.62 (2H, d, J = 8.9 Hz), 8.28 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.88, 45.63, 119.21, 123.84, 124.85, 126.22, 127.43, 127.74, 131.21, 132.24, 134.03, 148.77; HRFABMS. Calcd for $C_{25}H_{26}N_2$ (MH^+): 354.2096. Found: 354.2145.

1,6,28,33-Tetraaza[6.1.6.1]paranaphthalenophane (**13a**): Colorless amorphous solid (gradually colored green); mp 160°C< decomp (hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.83-1.95 (8H, m), 3.27~3.33 (8H, m), 4.62 (4H, s), 6.45 (4H, d, J = 8.0 Hz), 6.86 (3H, d, J = 8.0 Hz), 6.89 (1H, d, J = 8.0 Hz), 7.30-7.43 (8H, m), 7.80 (4H, d, J = 8.1 Hz), 7.98 (4H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.40, 43.57, 49.50, 104.57, 120.30, 123.91, 124.30, 124.72, 125.63, 127.72, 132.81, 142.00; HRFABMS. Calcd for $C_{50}H_{48}N_4$ (M^+): 704.3879. Found: 704.3896.

1,8,30,37-Tetraaza[8.1.8.1]paranaphthalenophane (**13b**): Colorless amorphous solid (gradually colored green); mp 160°C< decomp (hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55 (8H, br), 1.78 (8H, br), 3.25 (8H, t, J = 7.0 Hz), 4.63 (4H, s), 6.45 (4H, d, J = 7.8 Hz), 6.88 (4H, d, J = 7.8 Hz), 7.43

(8H, m), 7.84 (4H, m), 8.00 (4H, m); HRFABMS. Calcd for $C_{54}H_{56}N_4$ (M^+): 760.4505. Found: 750.4563.

1,13-Diaza[13.1]paranaphthalenophane (**12c**): Colorless amorphous solid (gradually colored green); mp 101-103°C (hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02-1.27 (14H, m), 1.56 (4H, quintet, J = 7.0 Hz), 3.38 (4H, t, J = 7.0 Hz), 4.67 (2H, s), 6.55 (2H, d, J = 8.0 Hz), 6.69 (2H, d, J = 8.0 Hz), 7.40-7.48 (4H, m), 7.84 (2H, d, J = 7.8 Hz), 8.08 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.23, 27.54, 28.72, 29.54, 30.19, 33.56, 43.93, 106.31, 120.55, 124.25, 124.65, 125.63, 125.97, 127.56, 133.16, 141.99; HRFABMS. Calcd for $C_{32}H_{38}N_2$ (M^+): 450.3035. Found: 450.3083.

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