

AMINOMETHYLATED HYDROXINAPHTHALENES: SYNTHESIS AND APPLICATION

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Abstract

The analysis of the literature is carried out and the results of the synthetic approaches to the aminomethylation of hydroxy derivatives of naphthalenes developed over the past 20 years are presented. Most of the described aminomethylation processes proceed as Mannich aminomethylation or, as a special case of a similar condensation — aminobenzylation according to Betti. The results of all studies are grouped according to the nature of the amine used in the synthesis: primary, secondary, tertiary. Most of the examples were considered for 2-naphthol, however, as the analysis of literature data shows, similar methods are applicable to 1-naphthol and dihydroxynaphthalenes with different positions of OH groups in the ring — often only the yields of the target product differ. Both the classical methods for the preparation of Mannich and Betti bases using the carbonyl component (formaldehyde, benzaldehyde and its derivatives, respectively) and special cases of synthesis, in which condensation is carried out by means of halogen derivatives, substituted azacrown ethers, etc., are presented. Particular attention is paid to the use of various catalysts and activators, allowing to significantly simplify the synthetic procedures and increase the yields of target compounds. The main fields of application of aminomethylated derivatives of hydroxynaphthalenes are presented

Keywords

Mannich aminomethylation, Betti aminobenzylation, primary amines, secondary amines, formaldehyde, 2-naphthol, dihydroxynaphthalenes

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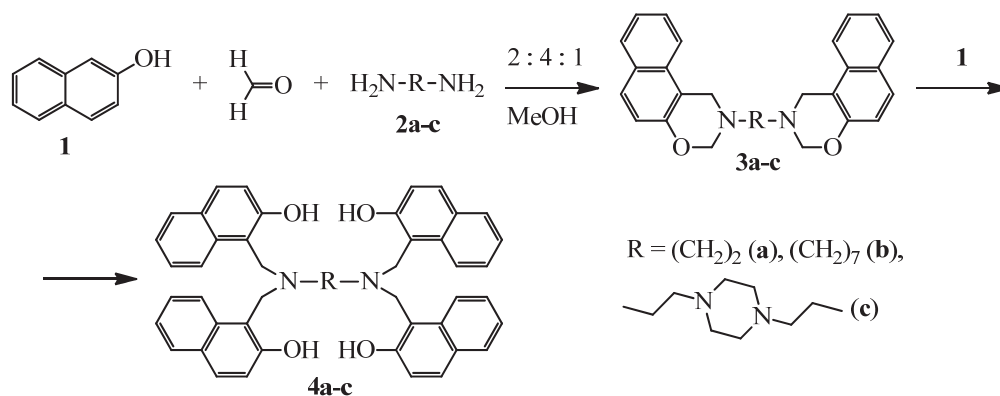
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Introduction. Since its discovery, the Mannich reaction [1] and Betti [2] reactions have been widely used in organic synthesis among the most convenient ways to create C–C bonds, which are also applicable for the series of condensed aromatic derivatives. Currently, aminomethylation has been

fairly well studied on 2-naphthol (β -naphthol), and in the last 20 years, a large number of studies have also appeared on the introduction of aminomethyl fragments into 1-naphthol (α -naphthol) and dihydroxynaphthalenes. It is known that the presence of aminomethyl groups in the structure of the molecules, especially those containing a heterocyclic fragment, leads to an increase in the physiological activity of the product [3–6]. Most often, aminomethylated derivatives of naphthalene systems are used as starting compounds of fine organic synthesis for the production of physiologically active substances [7–11], in the synthesis of homoisobioflavonoids [12], chromenes [13, 14], flavonoid analogues — enzyme inhibitors showing high activity [15–17], in the development of drugs with antiparasitic properties [18], new water-soluble inhibitors of tumor cell proliferation [19], ligands for the creation of complexes that are effective catalysts [20, 21] and contrasts in magnetic resonance imaging [22], as well as tautomeric switches [23].

Aminomethylation using primary amines. In most cases, the introduction of primary amines into aminomethylation pursues the goal of forming a six-membered oxazine ring with a functional substituent [24, 25]. Condensation of 2-naphthol **1** and formaldehyde with primary diamines **2a-c** at a reagent ratio of 2: 4: 1 yielded naphthoxazines **3a,b**, which, upon further interaction with 2-naphthol **1**, formed aminomethylated derivatives **4a-c** containing four residues of 2-naphthol in their structure [26]:

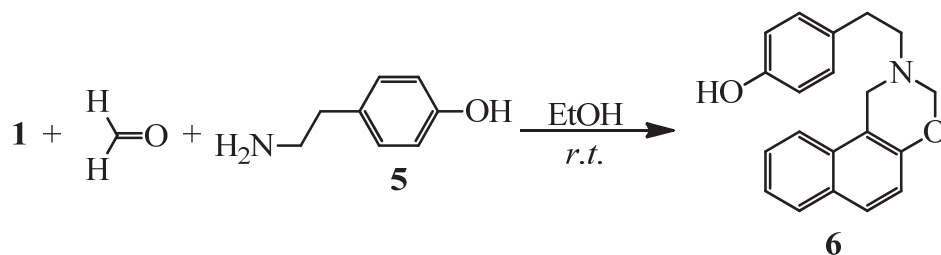


In case **3a, b**, the reaction proceeded in refluxing in methanol for 1 h with a yield of about 45 %, while **3c** was synthesized in 5 % yield in methanol with cooling. Further interaction of all naphthoxazines **3a-c** with 2-naphthol **1** proceeded at room temperature.

In general, the interaction of naphthoxazine derivatives with naphthols is a fairly common synthetic technique which was used previously for the synthesis of different compounds [27, 28]. The opening of the oxazine ring can also be

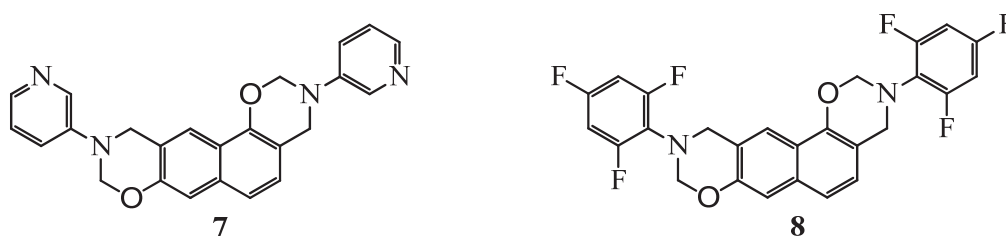
carried out by reaction with trimethylsilyl triflate by heating in toluene in the presence of tertiary amines [29].

The work [30] describes the preference of tyramines (β -(4-hydroxyphenyl) ethylamines) to bind with 2-naphthol **1** rather than undergo self-condensation.



This experimental fact is explained using semi-empirical and non-empirical calculations for complexes of so-called “macrocyclic templates” based on hydrogen bonds formed in solution as a transition state, in which 2-naphthol behaves as the most active reagent.

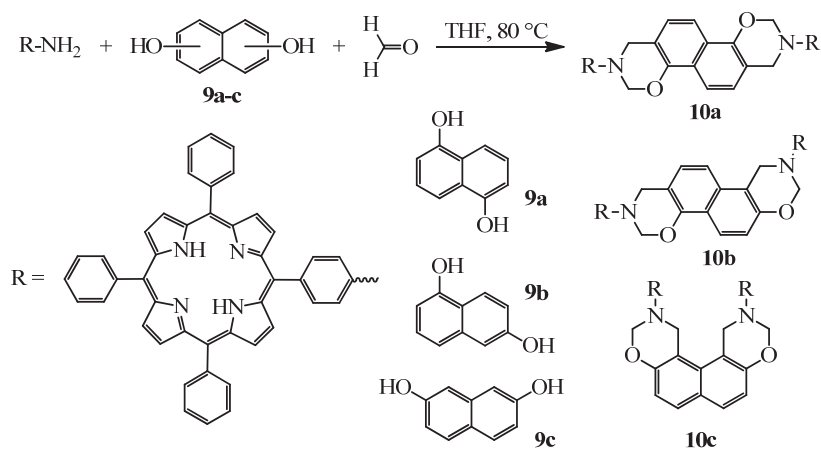
The reaction of 1,6-dihydroxynaphthalene with primary aromatic amines leads to dioxazines **7** [31] and **8** [32], and the closure of the oxazine ring occurs not in the fifth, but in the seventh position of the naphthalene ring.



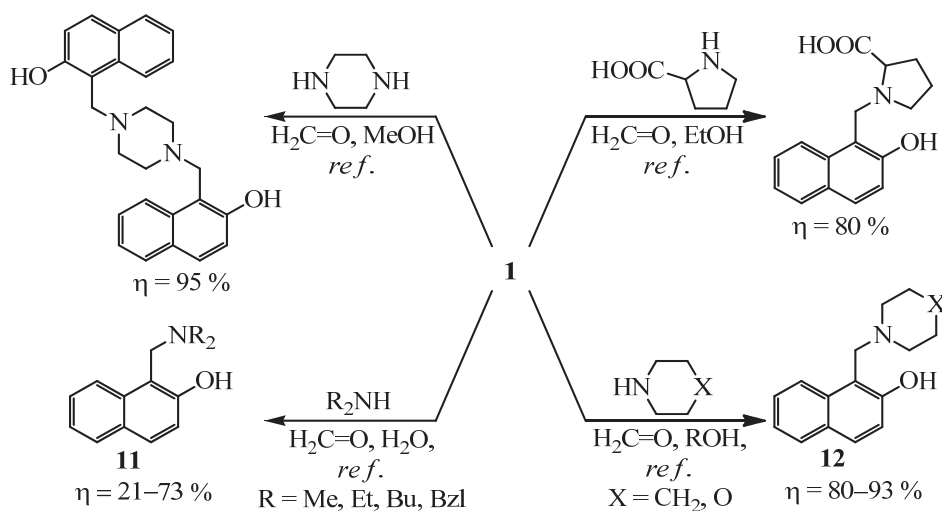
Aminomethylation of 1,6-dihydroxynaphthalene is carried out under harsher conditions than in the case of 2-naphthol **1** or 2,7-dihydroxynaphthalene.

Condensation of 1- and 2-naphthol, as well as various dihydroxynaphthalenes **9a-c** bearing remote OH-groups with monoaminotetraphenylporphyrin and formaldehyde, makes it possible to obtain various oxazinoporphyrins. Reactions proceed when boiling in THF for 24–30 h with yields of ~ 90 % (for monohydroxynaphthalenes) and ~ 40 % (for dihydroxynaphthalenes) [33].

It should be noted that in the case of 1,6-dihydroxynaphthalene **9b** in the reaction product **10b**, the oxazine ring closes to the fifth and sixth positions, in contrast to the results described in [34, 35].

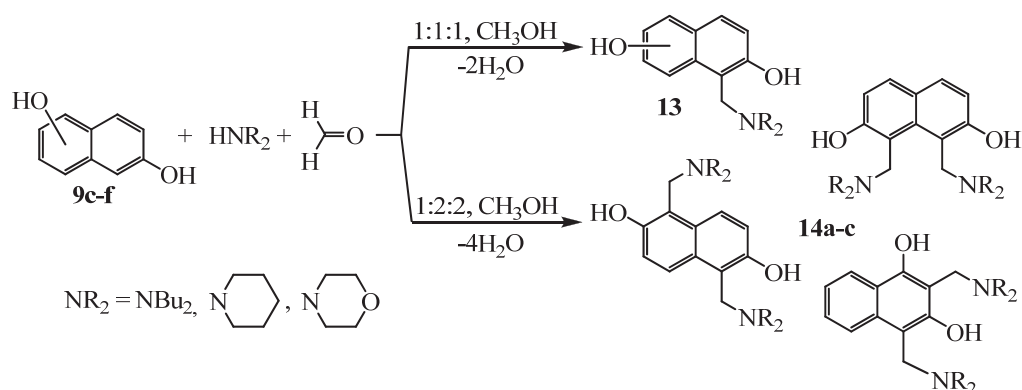


Aminomethylation using secondary amines. Despite the popularity of primary amines and the possibility of creating condensed rings on their basis, in most methods of aminomethylation of hydroxynaphthalene derivatives (1- and 2-naphthol, dihydroxynaphthalenes), various secondary amines of both aliphatic and heterocyclic series have been used over the past 20 years: dimethylamine [34–36], diethyl- and dibutylamines [37], dibenzylamine [37, 38], methylbenzylamine [38], heterocyclic pyrrolidine, piperidine, morpholine [37], piperazine [36, 39], amino acids [40], as well as amines containing complex substituents [20, 30]. In most cases, the reactions proceed at room temperature [30, 34–36, 38] or at the boiling point of solvents [20, 37, 39, 40], which are various alcohols, dichloromethane, and water. Aminomethylated products (Mannich bases) are formed in good yields (~ 80–95 %). Examples of reactions proceeding with 2-naphthol **1** are given below:



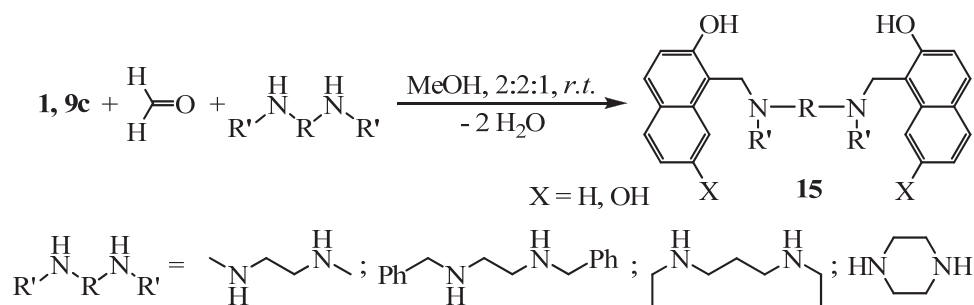
The processes listed above are also possible for 1-naphthol [35, 37, 38], but the yields of target products based on it, as a rule, are lower than those for 2-naphthol.

Dihydroxynaphthalenes (**9c-f**) can undergo both mono- and bisaminomethylation. 2,6-(**9d**), 2,7-(**9c**), and 1,3-(**9f**) Dihydroxynaphthalenes were introduced into the Mannich reaction, where dibutylamine, piperidine, and morpholine were used as the amine component. The reactions proceeded in methanol at room temperature [41–43].



In the case of cyclic amines, the reaction rate and product yield were much higher (> 80 %) than with dibutylamine. The yields of monoaminomethylated analogs **13** were slightly lower than their bisaminomethylated derivatives **14a-c** (> 80 % and > 92 %, respectively). It was noted that at any 1,3-dihydroxynaphthalene: formaldehyde: amine ratios, no monoaminomethylated derivatives were formed, which is probably due to the high reactivity of the hydrogen atoms of the aromatic ring at positions 2 and 4.

Using a similar procedure with diamines such as N,N'-dimethyl- and N,N'-dibenzylethylenediamines, N,N'-diethyl-1,3-propylenediamine and piperazine Mannich bases **15** were obtained in high yields (> 95 %), each containing two functionalized aromatic fragments — either 2-naphthol **1** or 2,7-dihydroxynaphthalene **9c** [44].



^1H NMR and IR spectra of derivatives **13** and **15** were affected by the intramolecular hydrogen bond $\text{O}-\text{H}\cdots\text{N}$: at $t = 22\text{ }^\circ\text{C}$, the ^1H NMR spectrum showed broadening of the signals of the protons of the piperidine, morpholine, or piperazine rings, respectively (2 in Fig. 1 *a*); however, when the sample was heated to $t = 80\text{ }^\circ\text{C}$ (*d*-DMSO), a narrow signal from the indicated protons appeared in the ^1H NMR spectrum, since at this temperature the hydrogen bond was broken (2 in Fig. 1 *b*).

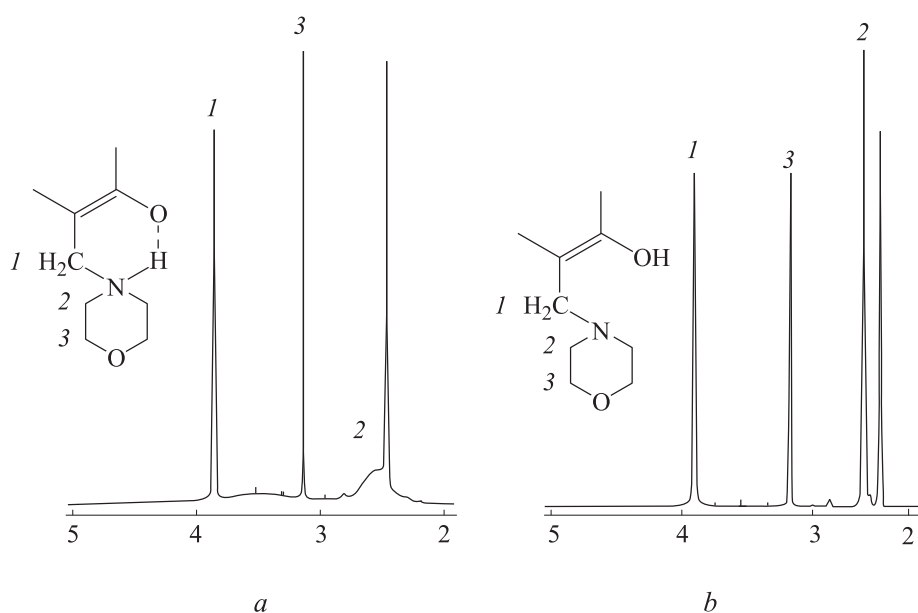


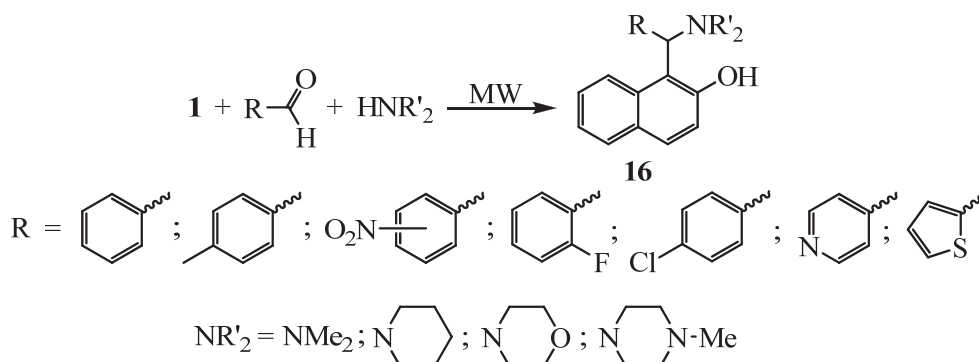
Fig. 1. Fragment of ^1H NMR spectrum (400 MHz, *d*-DMSO) of 1-morpholinomethyl-2,7-dihydroxynaphthalene **13**, recorded at: *a*) $t = 22\text{ }^\circ\text{C}$; *b*) $t = 80\text{ }^\circ\text{C}$ [43]

It is noted that bisaminomethylated dihydroxynaphthalenes bearing heterocyclic substituents demonstrate extremely low solubility in organic solvents (dioxane, acetonitrile, chloroform).

1,5- [35] and 2,3- [38] Dihydroxynaphthalenes were also subjected to bisaminomethylation, but the yields of the target products were lower than those of the aforementioned analogs.

In a number of studies, microwave irradiation was also used to intensify the process of introducing an aminomethyl group into the naphthalene ring [4, 34, 45]. The reactions were carried out without solvent and in the presence of *p*-toluenesulfonic acid as a catalyst; however, the yields of the target products were comparable to the classical methods. An undoubted advantage of this synthesis can be considered a significant reduction in the reaction time (from several hours to several minutes).

As can be seen, in all the described cases, formaldehyde was used as the carbonyl component. When the latter is replaced by an aromatic aldehyde, an aminoarylation reaction or Betti condensation takes place. Thus, the interaction of 2-naphthol **1** with secondary amines of various nature in the presence of aromatic aldehydes in a glycerol medium at a temperature of 90 °C [36], a water-ethanol mixture at room temperature [46] or under the action of microwave radiation (≈ 1 min) and the use of *p*-toluenesulfonic acid as a catalyst [45, 47] leads to the formation of derivatives **16**:



The yields of products **16** were in the range of 72–86 % depending on R.

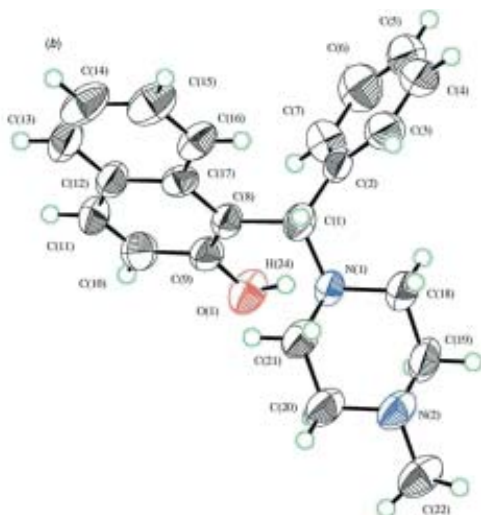


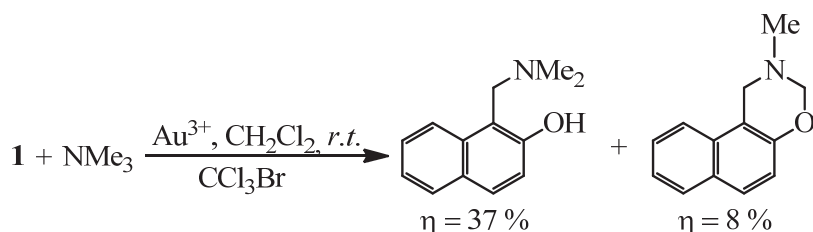
Fig. 2. Molecular structure of derivative **16** (R = Ph, NR₂ = N-methylpiperazine) [47]

Figure 2 shows the molecular structure of one of the products of the described condensation, where N-methylpiperazine was used as the amine component. X-ray diffraction analysis showed the presence of O–H···N hydrogen bonds, which stabilize the general configuration of the molecule, as was already noted for monoaminomethylated derivatives of dihydroxynaphthalenes [41–44].

The Mannich and Betti reactions can be carried out without using a solvent. For example, heating the mixture of 2-naphthol **1**, formaldehyde or benzaldehyde with various amines up to 60 °C for 1.5–2 h together with MgSO₄ [48] or at 40 °C for ~ 30 min using a heterogeneous catalyst nano-SiO₂–H₃BO₃ [49] yielded products **11**, **12**, **16**. The yields of the indicated

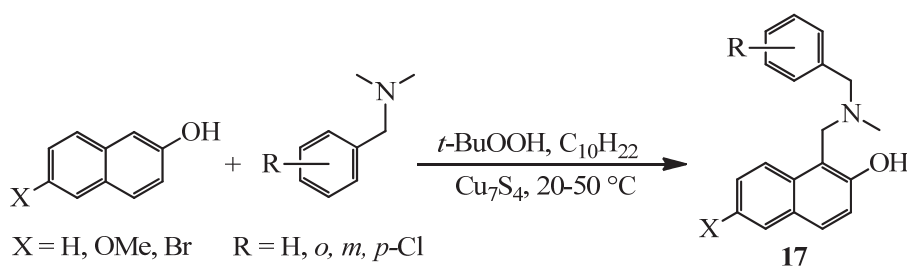
derivatives in the first case are comparable with the previously considered methods, while the product yields when using the nano-SiO₂-H₃BO₃ catalyst are always higher than 90 %.

Tertiary amines. Special cases of aminomethylation. The introduction of selective catalysts into the sphere of reaction or the presence of specific leaving groups in the starting materials make it possible to introduce tertiary amines into aminomethylation without using carbonyl derivatives. In the presence of catalytic amounts of Au(III) salts and CCl₃Br as an initiator, selective oxidative aminomethylation of 2-naphthol **1** with tertiary amines occurs at room temperature [50]:



In this case, a mixture of Mannich base with naphthoxazine is formed, and the yields of both are low.

Higher yields (72–80 %) of naphthalenes **17** selectively aminomethylated in *o*-position to OH-groups were obtained from 2-naphthol and its amphiphilic derivatives upon their oxidative heterogeneous coupling with tertiary amines in the presence of Cu₇S₄ nanoparticles [51].

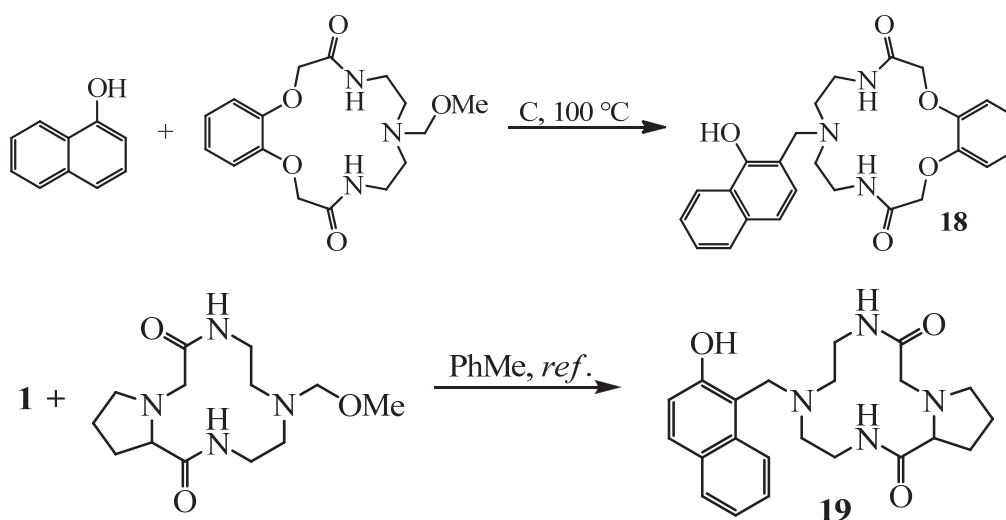


Product **17** (X = H, R = H) was also obtained via 2-naphthylboronic acid [52]. The reaction proceeded in water at 90 °C in the presence of *t*-BuOOH and NiCl₂ as a catalyst for 12 h with a yield of 74 %.

The use of triethylsiloxymethylamine (Et₃SiOCH₂NMe₂) also makes it possible to carry out aminomethylation without the participation of the carbonyl component with the formation of derivatives **11** [53]. The process takes place in benzene at room temperature for 20 min, but the yields with this synthesis method are much lower (57–73 %).

Environmentally friendly synthesis with the use of pincer complexes of Mn(I) [54] and Re(I) [55] involves the use methanol instead of aldehydes to obtain derivatives **11**, **12** and **16**. This process takes place in toluene at 120–130 °C for 16 h, and the product yields are either lower or comparable to the previously considered examples.

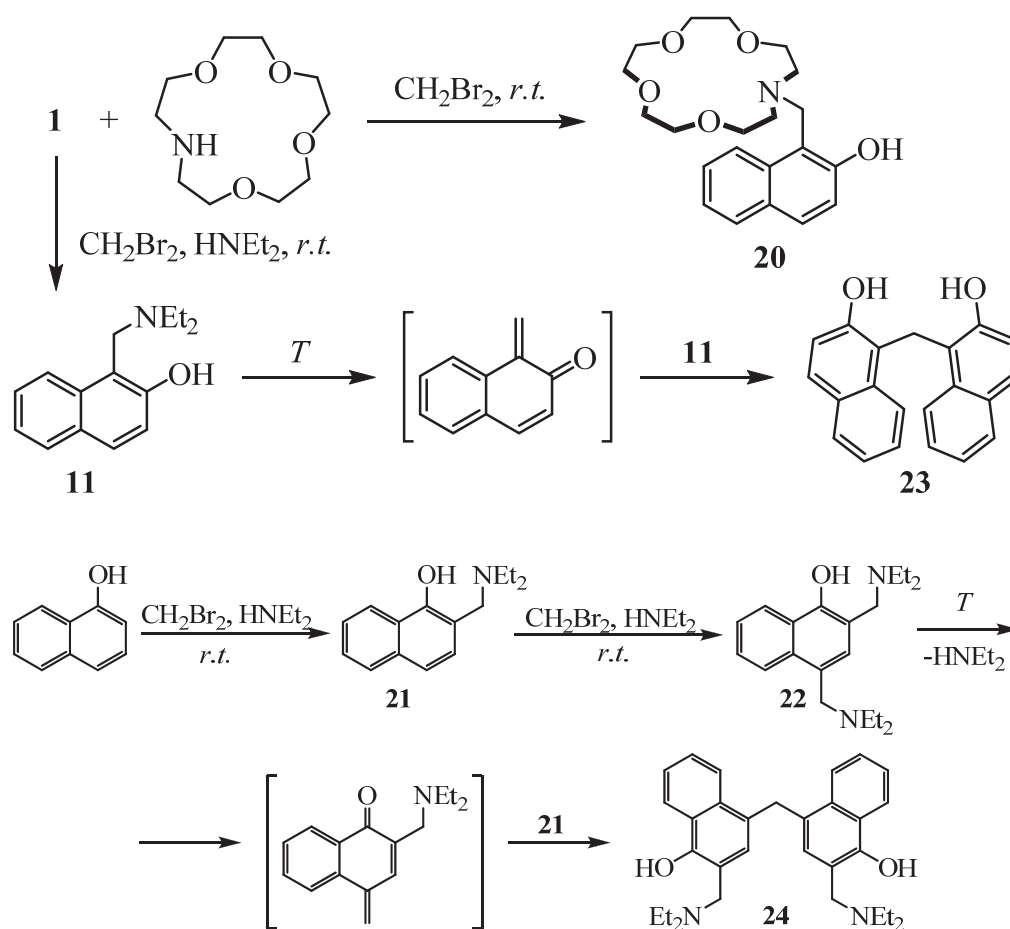
In the Mannich reaction, azacrown ethers can also be used as the amine component [3, 56, 57]. In this case, the process is also carried out without the participation of a carbonyl compound, using transesterification on graphite [3] or in a toluene solution [56] with strong heating:



In the first case, the yield of target products **18**, depending on the aromatic substituent (1- or 2-naphthols, hydroxyquinolines, substituted phenols) was 75–92 %, and in the second derivative **19** — only 74 %.

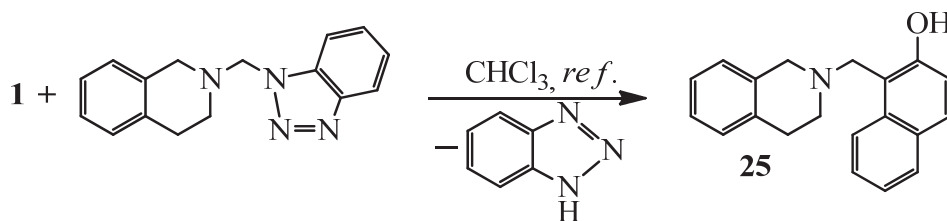
As already noted, in addition to formaldehyde, dichloro- and dibromo-methane can act as methylating reagents [57, 58]. When this reaction was carried out at room temperature, the yield of product **20** based on 2-naphthol was 74 %. Depending on the starting naphthol, when mono- (**11**, **21**) or diamino-methylated (**22**) products are heated to 110 °C, either 2,2'-dihydroxy-1,1'-dinaphthylmethane **23** or bisaminomethylated dinaphthylmethane derivative **24** can be obtained in 76 %.

The use of vanadium (IV) and (V) salts as catalysts makes it possible to carry out aminomethylation of 1- and 2-naphthol with amine N-oxides with the formation of derivatives **12** and **21** with good yields (58–92 %) [59]. The best results were shown by VO(acac)₂ (yield 92 % for 8 h of reflux in CH₂Cl₂, R = morpholine).

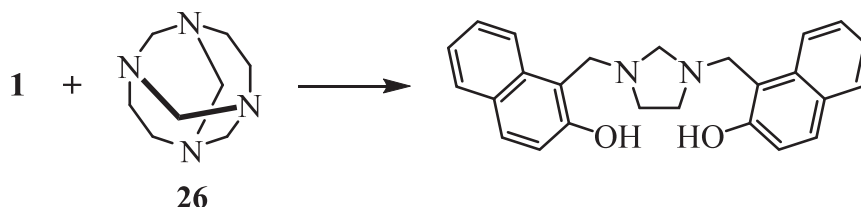


Similarly, the use of dimethylmethyleimine iodide in the interaction with 2-naphthol **1** in the presence of the $\text{Et}_3\text{N}-\text{MgCl}_2$ system in CH_2Cl_2 gives derivative **11** ($\text{R} = \text{Me}$) in quantitative yield [60].

The use of benzotriazoles, as an easily leaving group, allows the introduction of an aminomethyl fragment (derivatives of substituted tetrahydroisoquinoline) into the 2-naphthol **1** also without using the carbonyl component [61]. The process takes place for 24 h in boiling chloroform with the yield of the target product **25** over 90 %.



Aminomethylation with tetraazatricyclododecane (TATD) **26** and other polycyclic amines proceeds similarly without the use of carbonyl compounds [62–66]. For example, TATD reacts with 2-naphthol **1** under mild conditions: room temperature, water-dioxane solution, 1 day:



In the works it is noted that one of the key moments of such condensation is the activity of the α -protons of the naphthalene ring.

It was shown that such a reaction does not occur with the dibenzo analogue TATD **26**. A similar behavior is observed with bis(benzotriazoimidazoles): the reaction products are monoaminomethylated products **27** (Fig. 3) with a yield of no more than 47 % [63, 64]. Such reactions take place when heated in alcohols for several hours. Studying derivatives **27** by X-ray diffraction analysis showed the existence of strong intermolecular hydrogen bonds and the absence of intramolecular ones, as was noted in [41, 42, 44, 45, 47].

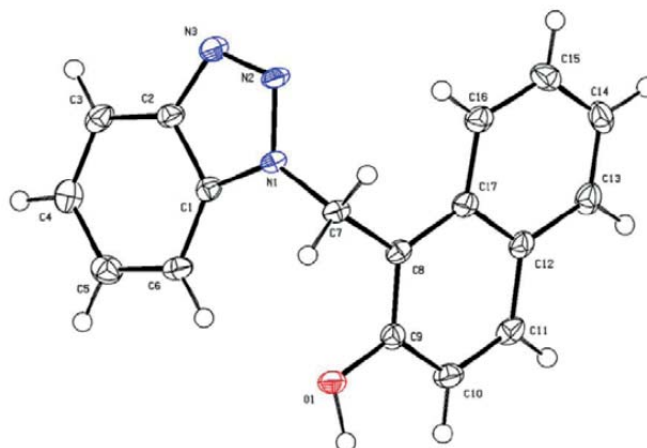


Fig. 3. Molecular structure of compound **27** [63]

Conclusion. The processes of aminomethylation and aminobenylation continue to be relevant and popular methods for creating C–C bonds in a series of condensed aromatic systems. With the development of synthetic approaches, the yields of the target products increase, the conditions become softer due to

the use of catalysts or the selection of appropriate solvents. At the same time, there is a constant and quite natural expansion of the areas of application of the Mannich and Betti bases.

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**«Физико-математические модели
и методы расчета воздействия
мощных лазерных и плазменных импульсов
на конденсированные
и газовые среды»**

Исследованы актуальные научные проблемы моделирования динамических процессов в экономических системах. Изложены основы моделирования динамики производственно-сбытовых и социально-психологических процессов взаимодействия экономических субъектов. Представлены разработанные авторами динамические модели, отражающие различные аспекты функционирования экономических систем в промышленности. Проанализированы прикладные аспекты использования инструментов системной динамики и агентного моделирования для исследования мультиагентного взаимодействия и проблем внедрения современных технологий цифрового производства.

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