A Simple and Effective Procedure for the *N*-Permethylation of Amino-Substituted Naphthalenes

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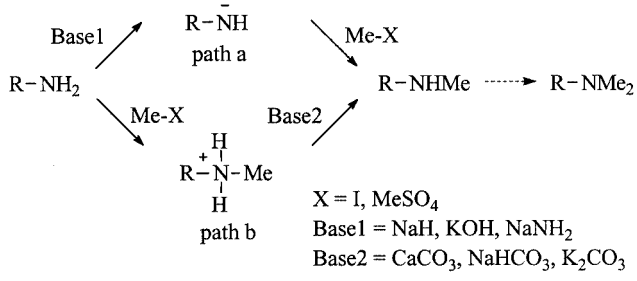
A wide range of amino-substituted naphthalenes can be *N*-permethylated by the system $Me_2SO_4/Na_2CO_3/H_2O$(alcohols) with good to excellent yields. Steric hindrance does not prevent the reaction. Some amines with electron-withdrawing groups, especially at nonconjugated positions, are also alkylated. The procedure allows the combination of a reduction (catalytic or by tin dichloride in acidic media) and a methylation in a one-pot process.

N-Peralkylated naphthylamines are very interesting and synthetically useful compounds, especially those bearing dialkylamino groups in *peri*-positions of the naphthalene ring, due to their high basicity (known as "proton sponges").[1] Two common approaches to the synthesis of such compounds and other *N*,*N*-dialkylarylamines from primary and secondary amines exist (Scheme 1; methylation, as the most routine procedure, is exemplified). The first one consists of an N−H bond ionization/alkylation sequence (Scheme 1, *path a*),[2] the main drawback of which is its inefficiency for amines with very low N−H acidity.[2f,2g] The second technique proceeds through a sequence of quaternization/deprotonation steps (*path b*),[3] which are most effective for amines with increased *N*-nucleophilicity. Moreover, alkylation by means of *path a*, despite its wide spread laboratory usage,[2] requires an inert atmosphere because highly reactive *N*-anions are generated during the reaction.



Scheme 1

Herein we propose a simple and effective system ($Me_2SO_4/Na_2CO_3/H_2O$) for the *N*-permethylation of different aminonaphthalenes at room temp. (20−25 °C). The reaction proceeds according to Scheme 1 (*path b*) and gives the best results with four equivalents of Me_2SO_4 and Na_2CO_3 per amino group of the starting amine (see Exp. Sect. for details). This is a modification of the method suggested earlier for several anilines and α- and β-aminonaphthalenes[3b] that was never adapted for arenes with several amino groups.

The results of *N*-permethylation of various naphthylamines with the system proposed and those for other alkylation methods are collected in Table 1. As one can see, this simple and cheap technique allows the methylation of a wide range of amines under very mild conditions with good to excellent yields. The only complications were observed in the case of tetraaminonaphthalenes: 1,4,5,8-tetraaminonaphthalene gave only tarry products, and 1,2,7,8-tetraaminonaphthalene is only alkylated in low yield (entry 8); and could not be solved by addition of a large excess of Me_2SO_4 and Na_2CO_3 (up to 10 equivalents of both these compounds per NH_2 group were tested) or increasing the reaction time. This can be attributed to the extremely fast oxidation of the corresponding tetraamines.

The position of the amino group (α or β) in the naphthalene core does not influence the rate and effectiveness of the reaction for simple amines (cf. entries 1, 2), although for polyamines with *peri*-NH_2 groups, the rate of the alkylation is somewhat faster for α-amino groups due to the formation of hydrogen-bond-stabilized cations such as **1** during the methylation process. This is illustrated by the methylation of 1,2,7,8-tetraaminonaphthalene. When the reaction is conducted for five, rather than ten, hours (entry 8), the ^{1}H NMR spectrum of the reaction mixture shows the presence of compounds **2**, **3** with partially methylated β-amino groups.

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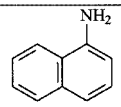
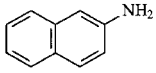
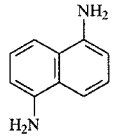
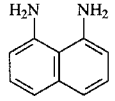
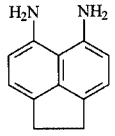
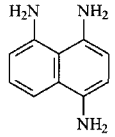
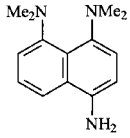
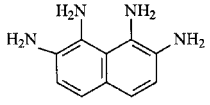
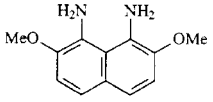
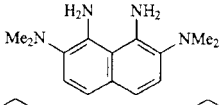
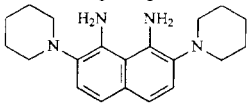
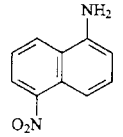
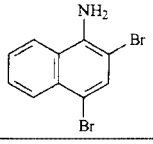
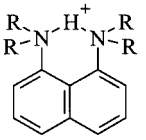
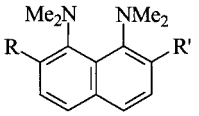
Table 1. Comparative results of exhaustive *N*-methylation of amino-substituted naphthalenes

Entry	Starting amine	Method/ reaction time[a]	Yield (%) [b]	Ref.
1		**A**/1.5h **B**/1h	81 90	[3b] [c]
2		**A**/45 min **B**/1h	98 91	[3b] [c]
3		**B**/2h **C**/8h **D**/2h	80[d] 20 84	[c] [3a] [2c]
4		**B**/2h **E**/3.5h **F**/3h	92 87 95	[c] [2a] [2b]
5		**B**/2h **F**/4h	90 94	[c] [2d]
6		**B**/2h **E**/3h	52[d] 60	[c] [2c]
7		**B**/2h **D**/2h	83[d] 87	[c] [2e]
8		**B**/10h	8[d]	[c]
9		**B**/5h **G**/20h	70[d] 40	[c] [2f]
10		**B**/5h **E**/17h	57[d] 7[d]	[c] [2g]
11		**B**/5h	39[d,e]	[c]
12		**F**/3h **H**/30h	36 81	[2h] [c]
13		**H**/45h	73	[c]

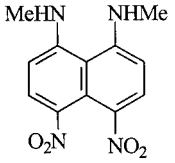
[a] **A**: $Me_2SO_4/NaHCO_3/H_2O$/10 °C; **B**: $Me_2SO_4/Na_2CO_3/H_2O$/room temp.; **C**: MeI/ $CaCO_3$/MeOH/H_2O/reflux; **D**: MeI/KOH/DMF/100 °C; **E**: Me_2SO_4/NaH/ THF/reflux; **F**: MeI/KOH/DMSO/100 °C; **G**: MeI/NaH/THF/reflux; **H**: Me_2SO_4/Na_2CO_3/MeOH/H_2O/room temp. [b] Isolated yield. [c] This work. [d] Yield from the corresponding nitro derivative. [e] Elemental analysis and spectroscopic data are consistent with the proposed structure. Full characterisation of the product will be described elsewhere.



1



2 R = R' = NHMe
3 R = NH_2, R' = NMe_2



4

The spatial proximity of the substituents does not prevent methylation by this method, but a longer time is needed to complete the reaction (entries 9, 10, 11).

It has repeatedly been stressed that *ortho*- and *peri*-substituted *N*,*N*-dimethylarylamines normally do not undergo quaternization or give unstable quaternary bases.[4] Even though the protocol employed is conducted entirely at room temp. and a rather large excess of Me_2SO_4 is used, the formation of quaternary salts of the amines is not a major process (see entries 2, 3, 7, 10).

In several cases the proposed procedure does not work properly even after prolonged stirring due to the low solubility of some of the amines. In order to increase their solubility and avoid this disadvantage, a large excess of Me_2SO_4 or a change of solvent from water to a water/methanol mixture (1:1) was attempted (entries 12, 13).

4-Nitro-α-naphthylamine, even in the presence of a 40-fold excess of dimethylsulfate in water/methanol and after stirring for 70 hours, gives a mixture of starting compound (44%) and *N*-methylated (45%) and *N*,*N*-dimethylated (11%) derivatives. Even more deactivated amino groups in compound **4** do not undergo quaternization at all.

Interestingly, certain amines bearing electron-withdrawing groups that are not conjugated with the amino groups also undergo methylation. Thus, 8-nitro-1-naphthylamine was solely converted into the corresponding *N*-permethylated derivative by this method with 90% yield.[5]

One of the useful features of our method is the possibility of combining the reduction of a nitro compound with the subsequent methylation of the resulting amine. Known alkylation techniques[2,3] require amines to be isolated after reduction of the nitro precursors as a change of solvent is sometimes needed[2,3] or the dry amines are necessary.[2] In our case, the reduction and the methylation steps can be merged, especially when the nitro compound is reduced by tin dichloride in an acidic medium. After completion of the reduction, the pH of the resulting mixture was made neutral, and the methylation agent and the base were introduced directly into the reaction mixture. The effectiveness of this one-pot procedure is the same or higher than in the traditional two-step approach. For example, 1,2,7,8-tetraaminonaphthalene (entry 8) can be obtained either by catalytic hydrogenation in methanol or reduction of 2,7-diamino-1,8-dinitronaphthalene by tin dichloride. In the first case, after the isolation of the amine followed by methylation, the yield of 1,2,7,8-tetrakis(dimethylamino)naphthalene is 5%. Using the tin dichloride reduction and the one-pot procedure, the compound is obtained in 8% yield. For 1,4,5-triaminonaphthalene the yields are 50 and 52%, respectively. Generally

all peralkylations of the amines presented in the table can be performed in such a way.

Alkylation with Me_2SO_4 can be conducted entirely in alcohols instead of water with the same efficiency. This peculiarity is important when combining catalytic hydrogenation and methylation because hydrogenation reactions are generally performed in alcohols. In this case, a longer reaction time is required. For example, α-aminonaphthalene is converted into the corresponding *N*,*N*-dimethyl derivative in one hour in water (entry 1) whereas the same reaction requires four hours in methanol; methylation of 1,8-diaminonaphthalene takes six hours (compare with entry 4) and addition of water decreases the reaction time.

Finally, the protocol described here opens new horizons for the synthesis of previously mal- or inaccessible polyfunctional arylamines. We hope that this method, which is an excellent complement to the well-known techniques, will find a wide application in the synthesis of "proton sponge"-like compounds and other peralkylated arylamines.

Experimental Section

General Methylation Procedure: Me_2SO_4 (freshly distilled; 4 mmol per amino group) followed by 5 mL of water (alcohol) and $Na_2CO_3 \cdot 10H_2O$ (in a quantity equimolar to Me_2SO_4) were added to 1 mmol of amine. The reaction mixture was stirred well (CO_2 evolution!) for the appropriate time (see Table 1; TLC control). The reaction mixture was then basified with 20% KOH to a strongly basic pH of 11−13, and the methylation products were extracted with benzene and purified either by crystallisation or by chromatography on alumina. Spectroscopic and physical properties of all methylated products are identical with those of authentic samples.

Acknowledgments

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