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NEW METHOD FOR THE DIRECT ELECTROPHILIC AMINATION OF AROMATIC COMPOUNDS AND ITS USE IN THE ANNELATION OF THE PYRIMIDINE RING

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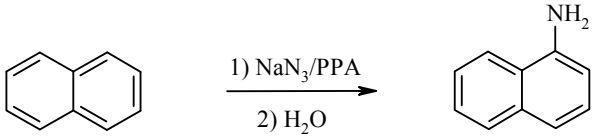
A method has been developed for the synthesis of aromatic amines by the amination of the corresponding aromatic compounds using sodium azide in PPA. A method for the synthesis of quinazolines and benzo[h]quinazolines using this reaction and the subsequent reaction of the intermediates with 1,3,5-triazines has been developed.

Keywords: sodium azide, arenes, aromatic amines, benzo[*h*]quinazolines, perimidines, PPA, 1,3,5-triazines, quinazolines, amination.

In previous work [1, 2], we discovered a new reagent system for the electrophilic amination of aromatic compounds and shown its applicability for perimidines. In the present work, we have extended this method for the synthesis of other aromatic amines and shown its applicability in combination with 1,3,5-triazines for the annelation of the pyrimidine ring to aromatic compounds.

As noted in our previous work [1, 2], the reaction of perimidines with a threefold excess of PPA at 80-90°C leads to the corresponding 6(7)-aminoperimidines in high yield. The PPA sample used containing 86% P_2O_5 was obtained according to Uhlig [3].

We might have assumed that this reagent system would be applicable for the amination of other aromatic compounds. Indeed, we showed that the reaction proceeds analogously with naphthalene to give 1-naphthylamine (**2a**) in 31% yield. The low yield is mostly a consequence of sublimation of naphthalene from the reaction mixture.



1a **2a**

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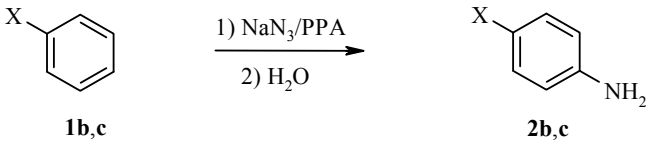
The reaction proceeds with much greater facility with anisole **1b** and phenol **1c**. A 1.1-fold excess of sodium azide is sufficient for PPA with 86% P_2O_5 content, while a 1.5-fold excess is sufficient for PPA with 80% P_2O_5 content. A lower temperature of 66-60°C is required. The yield of *p*-anisidine (**2b**) was 86%, while the yield of *p*-aminophenol **2c** was 74%.

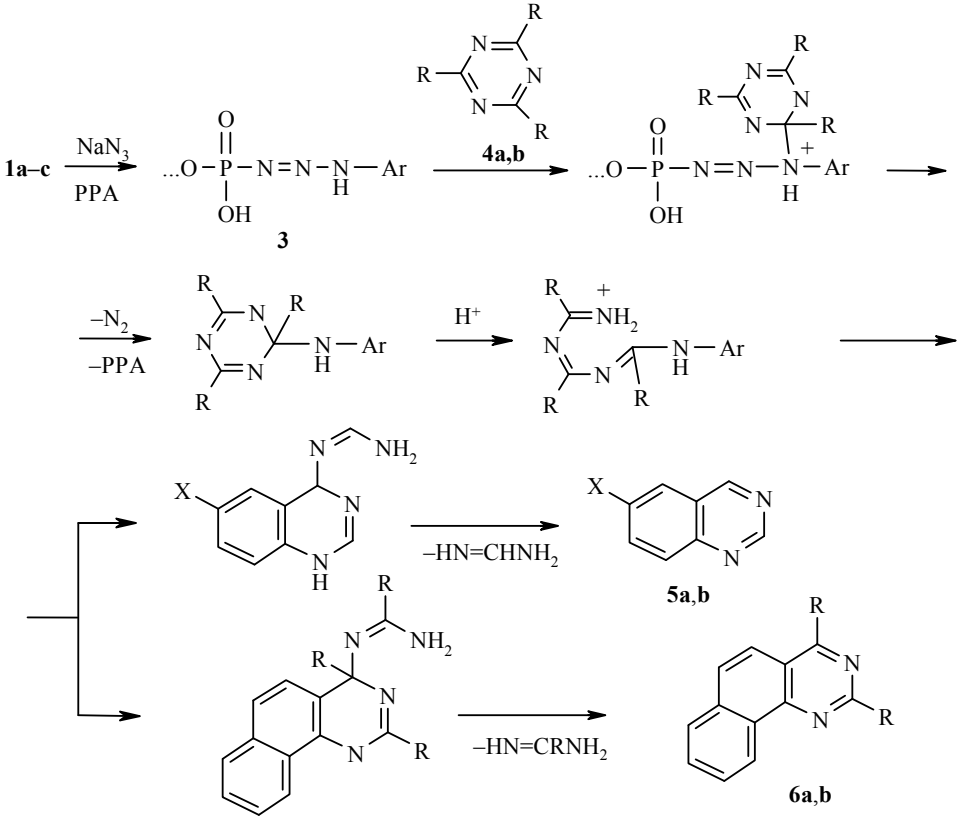


1b,**c** **2b**,**c**

1, **2 b** X = OMe, **c** X = OH

The reaction does not proceed at all with arenes containing weaker electron-donor substituents such as toluene or acetanilide.

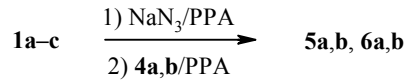
The reaction mechanism is probably analogous to the mechanism presented in our previous work [1, 2] and involves the formation of intermediates **3**, which presumably may not only undergo protonation but also react with other electrophilic reagents such as 1,3,5-triazines. In this case, the reaction should proceed as shown in the following scheme.



4, 6 a R = H, **b** R = Me; **5 a** X = OMe, **b** X = OH; Ar = 1-$C_{10}H_7$, 4-$MeOC_6H_4$, 4-HOC_6H_4

1,3,5-Triazine (**4a**) is added to the reaction mixture obtained from anisole **1b** or phenol **1c** and heated for 4 h at 90-100°C to give quinolines **5a,b*** in 54% and 49% yield respectively.

* Reported in our preliminary communication [4].



1a–c → **5a**,**b**, **6a**,**b**

The reaction proceeds similarly if naphthalene **1a** is used as the starting compound.

Thus, a convenient method has been developed for the amination of aromatic compounds. An advantage of this method is the possibility of its combination with ring annelation. In this work, we have demonstrated the feasibility of annelating the pyrimidine ring to benzene and naphthalene.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WP-200 spectrometer at 200 MHz with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 3:1 ethyl acetate–ethanol as the eluent.

A commercial sample of 1,3,5-triazine (**4a**) was obtained from Aldrich, while 2,4,6-trimethyl-1,3,5-triazine (**4b**) was prepared according to Schaefer [5].

Amination of Aromatic Compounds (General Method). A mixture of corresponding aromatic compound **1a-c** (1 mmol), sodium azide (in the case of naphthalene **1a**, 0.195 g, 3 mmol) or (in the case of arenes **1b** and **1c**, 0.071 g, 1.1 mmol) in PPA (2-3 g) was heated to 75-80°C (in the case of naphthalene **1a**) or 55-60°C (in the case of the other arenes) with vigorous stirring for 5 h. The reaction mixture was treated with 50 ml water, filtered, and extracted with three 50-ml ethyl acetate portions. The aqueous layer was brought to pH 9-10 by adding ammonium hydroxide. The precipitate or oil formed was extracted with three 50 ml ethyl acetate portions. The solvent was evaporated off. The residue was dissolved in 5 ml ethanol and the solution obtained was saturated with dry gaseous HCl. The precipitate formed of the hydrochloride salt was purified by recrystallization from ethanol.

1-Naphthylamine (2a) was obtained in 34% yield (0.049 g); mp 48-50°C (mp 48-49°C [6]). ^{1}H NMR spectrum in $CDCl_3$, δ, ppm (*J*, Hz): 4.09 (2H, br. s, NH_2); 6.80 (1H, dd, *J* = 6.6, *J* = 1.8, H-4); 7.31-7.41 (2H, m, H Ar); 7.46-7.54 (2H, m, H Ar); 7.80-7.89 (2H, m, H Ar). Found, %: C 84.02; H 6.27; N 9.71. $C_{10}H_9N$. Calculated, %: C 83.88; H 6.34; N 9.78.

4-Anisidine (2b) was obtained in 86% yield (0.106 g); mp 57-59°C (mp 56-59°C [7]). The ^{1}H NMR spectrum was identical to the spectrum given by Casarini [7].

4-Aminophenol (2c) was obtained in 74% yield (0.081 g); mp 188-191°C (aqueous ethanol) (mp 187-190°C [8]). Hydrochloride salt: mp 240-242°C (ethanol). ^{1}H NMR spectrum in DMSO-d_6, δ, ppm (*J*, Hz): 6.87 (2H, d, *J* = 7.6, H-3,5); 7.21 (2H, d, *J* = 7.6, H-2,6); 9.88 (1H, br. s, OH); 10.19 (3H, br. s, NH_3).

Synthesis of Quinazolines 5a and 5b and Benzo[*h*]quinazolines 6a,**b (General Method)**. A mixture of aromatic compound **1a-c** (1 mmol), sodium azide (0.195 g, 3 mmol, in the case of naphthalene **1a**) or (0.071 g, 1.1 mmol, in the case of arenes **1b** and **1c**) in PPA (2-3 g) was heated at 75-80°C (in the case of naphthalene **1a**) or 55-60°C (in the case of the other arenes) with vigorous stirring for 5 h. Then, the temperature was raised to 90-100°C, corresponding triazine **4a** or **4b** (1.1 mmol) was added, and stirring was continued at this temperature for 5 h. The reaction mixture was treated with 50 ml water, filtered, and extracted with three 50-ml ethyl acetate portions. The solvent was evaporated off and the residue was purified by recrystallization or sublimation.

6-Hydroxyquinazoline (5a) was obtained in 49% yield (0.072 g); mp 237-239°C (water) (mp 239°C [9]). The ^{1}H NMR spectrum was given in our previous work [4].

6-Methoxyquinazoline (5b) was obtained in 54% yield (0.086 g); mp 71-72°C (petroleum ether) (mp 71°C [9]). The ^{1}H NMR spectrum was given in our previous work [4].

Benzo[*h*]quinazoline (6a) was obtained in 26% yield (0.047 g); mp 101-103°C (chloroform–ethanol) (mp 102-103°C [10]). The ^{1}H NMR spectrum corresponded to the spectrum given by Koyama et al. [10].

2,4-Dimethylbenzo[*h*]quinazoline (6b) was obtained in 22% yield (0.046 g); mp 119-121°C (ethanol) (mp 119-121°C [11]). The ^{1}H NMR spectrum corresponded to the spectrum given by Petterson et al. [11].

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