Formation of anilines from 5-nitro-2-phenylpyrimidine, amines, and acetone

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The reaction of 5-nitro-2-phenylpyrimidine with aliphatic amines and acetone gave *N*-substituted 4-nitroanilines. In addition, 2-methyl-5-nitropyridine was also obtained from ethylamine.

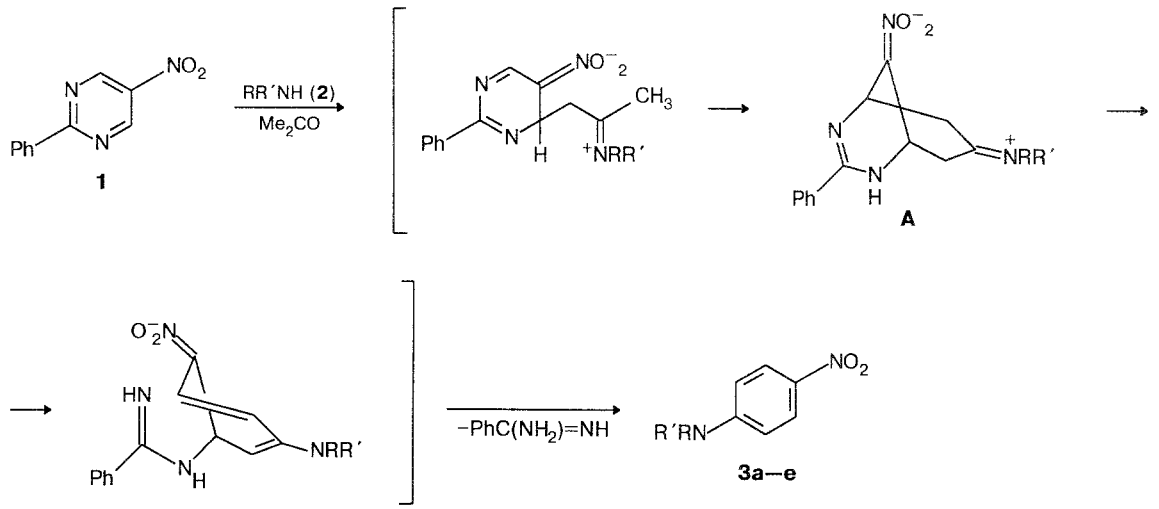
Key words: pyrimidine; transformation of cyclic intermediates; anilines; pyridine.

Previously,[1,2] we have suggested that the transformation of *symm*-triazine to derivatives of pyridine and pyrimidine, which occurs when it is treated with ketone-derived enamines, proceeds mainly as electrocyclic opening of the triazine ring after the addition of a C-nucleophile. Another pathway, involving intermediate adducts in which both nucleophilic atoms of acetone are attached to the heterocyclic ring, has been suggested to explain the unusual reaction of indolization of nitropyridinium salts discovered by us.[3] In the series of electron-deficient azines, pyrimidine derivatives display intermediate properties in reactions with nucleophiles. Typically, they undergo nucleophilic addition at positions 4, 6, and 2. The action of such nucleophiles as the hydroxyl anion, the amide ion, and amines, which eventually can result in recyclization, simple opening of the pyrimidine ring, or ring opening followed by hydrolytic cleavage to low-molecular products, has been studied the most extensively. The reactions of pyrimidine derivatives with C-nucleophiles have been studied much less thoroughly.[4]

It was of interest to elucidate the regularities of the reaction of nitro pyrimidines with acetone and amines. Such a study might provide valuable information about the ability of heterocyclic systems, other than the pyridine system, to undergo processes of ring formation, rearrangement, and fragmentation ("cyclotransformation") in the presence of acetone, a molecule with two nucleophilic carbon atoms.

It was found in this work that the treatment of 5-nitro-2-phenylpyrimidine (**1**) with acetone and aqueous solutions of alkyl amines or dimethylamine (**2**) at

Scheme 1



R = H; R′ = Me (**a**); R′ = Et (**b**), R′ = *n*-Bu (**c**), R′ = *s*-Bu (**d**); R,R′ = Me (**e**)

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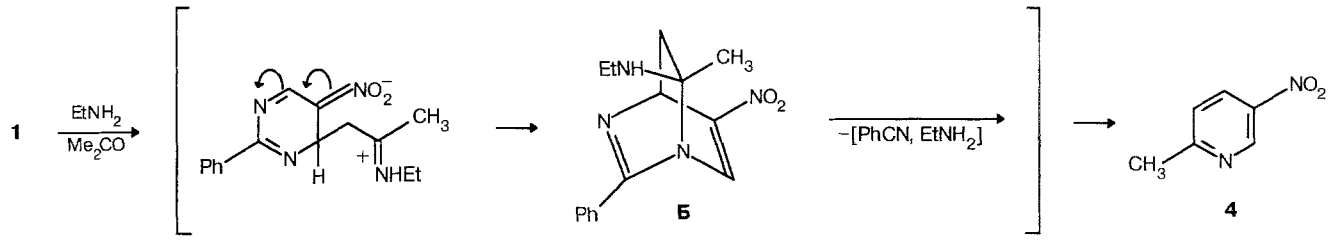
Scheme 2



room temperature results in the corresponding *N*-substituted 4-nitroanilines (**3a—e**) in up to 30 % yields.

It is known that the reaction of 5-nitro pyrimidine derivatives with acetone in the presence of strong bases results in anionic σ-complexes,[5] which are also the likely intermediates in the recyclization of compound **1**. It is also possible that initially the condensation of **1** with the acetone enamine occurs. On the other hand, numerous examples are known of the formation of bicyclic adducts in reactions of derivatives of trinitrobenzene and dinitropyridine with ketones.[6] The structures of these compounds have been reliably proven. There is sufficient evidence to interpret our data in a similar way, although we could not obtain any direct evidence of the formation of compounds of type **A** (Scheme 1).

Probably, the final step of the reaction involves the aromatization of the benzene ring through the elimination of benzamidine. This gives nitroanilines **3**, just as the cyclotransformation of *symm*-triazine into 4-aminopyridines when it is treated with enaminones is accompanied by the formation of formamidine.[1]

Elongation of the alkyl chain, its branching, or the use of dimethylamine instead of an alkylamine, *i.e.*, an increase in the role of the steric factor, slow down the process and somewhat decrease the yields due to concurrent polycondensation processes.

When we analyzed the products of the reaction of compound **1** with ethylamine and acetone, we could also isolate, in addition to aniline **3b**, 2-methyl-5-nitropyridine (**4**), although its yield was only 4 %. The formation of compound **4** can be explained by the fact that nitropyrimidine **1** is probably activated not only toward nucleophilic attack by the β-carbon atom of acetone enamines, but also toward cycloaddition by the reverse Diels—Alder reaction, as we have proposed previously[2] to explain the cyclotransformation of *symm*-triazine into pyrimidine derivatives. The bicyclic adduct **B** then eliminates benzonitrile and ethylamine fragments to give pyridine **4** (Scheme 2).

Thus, the hitherto unknown reaction of a nitro derivative of pyrimidine with aliphatic amines and acetone can involve both the C—C—C triad of atoms and two C—C atoms of acetone to give derivatives of benzene and pyridine, respectively. On the other hand, the reaction found in this work formally provides one more method for the synthesis of anilines.

Experimental

The reactions were monitored by TLC on Silufol UV-254 plates. Authentic samples were used for chromatographic comparison with the compounds obtained.

General procedure for the synthesis of *N*-alkyl- and *N,N*-dialkyl-4-nitroanilines (3). A 25—30 % solution of an amine (3.5 mL) and Me_2CO (0.15 mL, 2 mmol) were added with stirring to 5-nitro-2-phenylpyrimidine (0.1 g, 0.5 mmol). The mixture was kept at ~20 °C for a week and then extracted with benzene. The extract was dried with $MgSO_4$ and evaporated to dryness. The compound obtained was purified on a column with silica gel (L—100/160 μ) in $CHCl_3$.

***N*-Methyl-4-nitroaniline (3a)** was obtained as described above from compound **1**, Me_2CO, and aqueous $MeNH_2$. The yield of compound **3a** was 30 %, m.p. 148—149 °C (*cf.* Ref. 7: m.p. 148—149 °C).

***N*-Ethyl-4-nitroaniline (3b) and 2-methyl-5-nitropyridine** were obtained similarly from compound **1**, Me_2CO, and aqueous $EtNH_2$. The yield of compound **3b** was 24 %, m.p. 93—95 °C (*cf.* Ref. 8: m.p. 93—95 °C). The yield of compound **4** was 4 %, m.p. 110—112 °C (*cf.* Ref. 9: m.p. 110—112 °C).

***N*-Butyl-4-nitroaniline (3c)** was obtained from compound **1** (0.1 g, 0.5 mmol), Me_2CO (6 mL), and *n*-$BuNH_2$ (0.3 mL, 3 mmol). The reaction mixture was kept for one week, evaporated to dryness, and treated according to the general procedure. The yield of compound **3c** was 16 %, m.p. 54—55 °C (*cf.* Ref. 10: m.p. 56—57 °C).

***N*-(*sec*-Butyl)-4-nitroaniline (3d)** was obtained similarly to compound **3c** from compound **1** (0.1 g, 0.5 mmol), Me_2CO (6 mL), and *sec*-$BuNH_2$ (0.3 mL, 3 mmol). The yield of compound **3d** was 14 %, m.p. 39—40 °C (*cf.* Ref. 10: m.p. 40 °C).

***N,N*-Dimethyl-4-nitroaniline (3e)** was obtained from compound **1**, Me_2CO, and aqueous Me_2NH. The yield of compound **3e** was 7 %, m.p. 159—160 °C (*cf.* Ref. 11: m.p. 159—160 °C).

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