Preparative synthesis of 4,6-dinitroanthranil*

*V. V. Mezhnev, M. D. Dutov, and S. A. Shevelev**

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
E-mail: shevelev@ioc.ac.ru

A preparative method for the synthesis of 4,6-dinitroanthranil by intramolecular cyclization of 2-azido-4,6-dinitrobenzaldehyde was developed.

Key words: 2,4,6-trinitrotoluene, 2,4,6-trinitrobenzaldehyde, 4,6-dinitroanthranil.

Benzo[*c*]isoxazoles (also known as 2,1-benzoisoxazoles or anthranils) are widely used in organic synthesis, including the synthesis of valuable biologically active compounds.[1] Among nitro-containing anthranils, 4,6-dinitroanthranils are of particular interest because the benzene fragment can be functionalized not only *via* modification of the nitro groups or their *ipso*-substitution but also *via* nucleophilic substitution of hydrogen (S_N^H) that is *ortho* to the nitro group, which is facilitated by the formation of stable anionic σ^H-adducts of nucleophiles with the benzene ring.[2—6] Some 3-substituted 4,6-dinitroanthranils have been described.[7,8] However, the first member of the series (3-unsubstituted 4,6-dinitroanthranil) remains virtually inaccessible. In some cases, 4,6-dinitroanthranil has been detected among other reaction products, though in very low yields.[9—11] It has been reported[12] that 4,6-dinitroanthranil can be obtained in 60% yield from picryl chloride like 6-nitroanthranil from 1-chloro-2,4-dinitrobenzene. Unfortunately, the experimental procedure has been omitted.

We assumed that thermolysis of 2-azido-4,6-dinitrobenzaldehyde **1** would be a convenient preparative route to 4,6-dinitroanthranil **2** (Scheme 1).

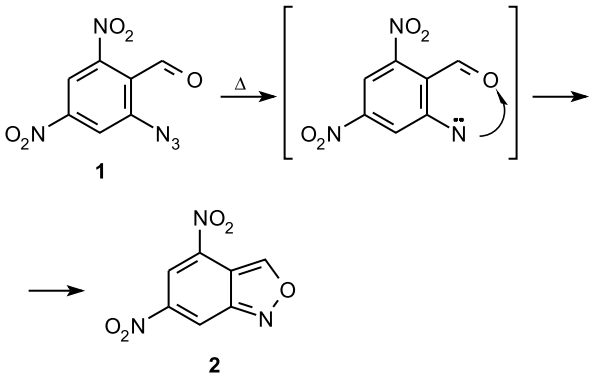
In an attempted selective synthesis of azide **1**, we studied the regioselectivity of a reaction of 2,4,6-trinitrobenzaldehyde **3** (see Ref. 13) with NaN_3 (Scheme 2).

According to the data obtained (Table 1), the displacement of the nitro group by NaN_3 from aldehyde **3** is not selective: the reaction always gives a mixture of 2-azido-4,6-dinitrobenzaldehyde **1** and its *para*-isomer 4-azido-2,6-dinitrobenzaldehyde **1′**. Their ratio depends on the solvent and the catalyst.

In less polar solvents, the yield of the *ortho*-product increases. The maximum ratio *ortho* : *para* = 4 : 1 was achieved in THF at room temperature (entry *2*) and in boiling benzene in the presence of 5% $Et_3N \cdot HCl$ (entry *4*).

The reaction in diethyl ether in the presence of 5% 18-crown-6 predominantly gives the *para*-product. This unexpected outcome can be attributed to the formation of a too bulky solvate pair strongly shielding the *ortho*-nitro group and preventing its displacement.

Scheme 1



Scheme 2

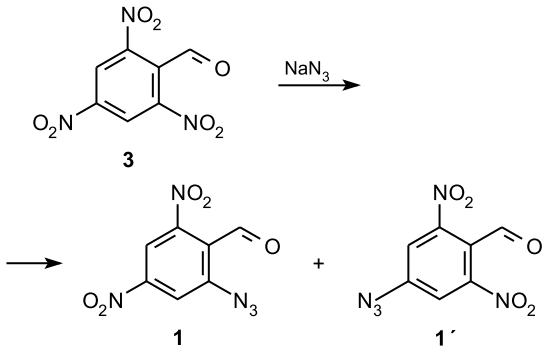


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Table 1. Displacement of the nitro group from 2,4,6-trinitrobenzaldehyde **3** under the action of NaN_3

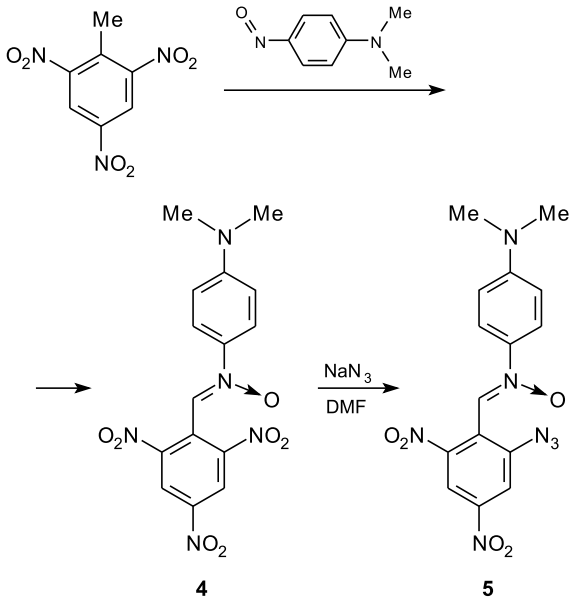
Entry	Solvent	Catalyst	*T*/°C	*t*/h	Ratio of isomers *ortho* : *para*
1	DMF	—	20	1	2 : 1
2	THF	—	20	50	4 : 1
3	THF	$Et_3N \cdot HCl$	20	20	1 : 1
4	PhH	$Et_3N \cdot HCl$	80	15	4 : 1
5	Et_2O+EtOH	—	20	25	2.5 : 1
6	Et_2O	18-crown-6	20	10	1 : 4

Reflux of a mixture of *ortho*-/*para*-azidodinitrobenzaldehydes in toluene gives 4,6-dinitroanthranil **2**, which can be isolated by column chromatography. Thus, this synthesis of 4,6-dinitroanthranil **2** cannot be regarded as a preparative one because of the insufficiently selective azidation of 2,4,6-trinitrobenzaldehyde **3**.

At the same time, it has been demonstrated[14,15] that the precursor of trinitrobenzaldehyde **3**, *viz.*, 4-(*N*′,*N*′-dimethylamino)-*N*-(2,4,6-trinitrobenzylidene)aniline *N*-oxide (**4**) prepared by condensation of 2,4,6-trinitrotoluene with *N*,*N*-dimethyl-4-nitrosoaniline, regiospecifically reacts with NaN_3 in DMF at ~20 °C: only the 2-NO_2 group is displaced to give *N*-(2-azido-4,6-dinitrobenzylidene)-4-(*N*′,*N*′-dimethylamino)aniline *N*-oxide (**5**) in 85% yield (Scheme 3)*.

We found that acid hydrolysis of azide **5** in toluene with conc. HCl at ~20 °C followed by *in situ* reflux of intermediate 2-azido-4,6-dinitrobenzaldehyde **1** affords 4,6-dinitroanthranil **2** in 76% yield (with respect to azide **5**) (Scheme 4). After the reaction is completed, anthranil **2** is in the organic layer (toluene), while a second hydrolysis product, *viz.*, substituted phenylhydroxylamine (**6**), is mostly in the acid layer.

Scheme 3



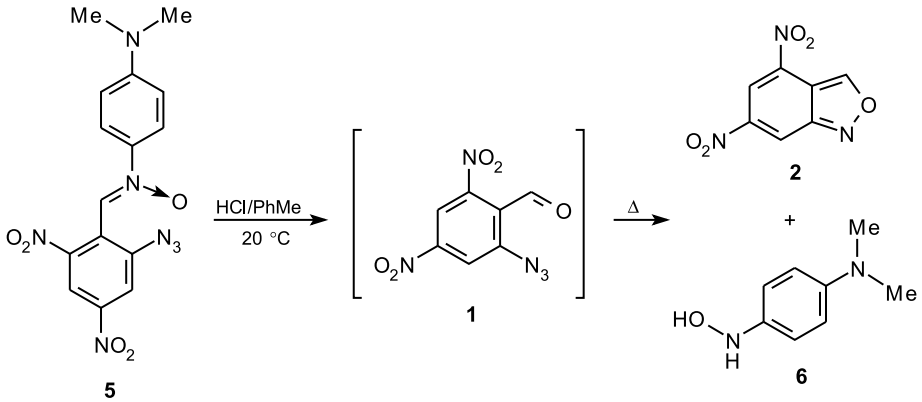
Thus, we developed a preparative method for the synthesis of 4,6-dinitroanthranil **2**.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 and Bruker WM 250 instruments, respectively. Chemical shifts δ are referenced to $SiMe_4$. Mass spectra were recorded on a Kratos MS-30 instrument (70 eV). Melting points were measured on a Boetius hot stage (Kofler technique, heating rate 4 deg min^{-1}).

4,6-Dinitroanthranil (2). Concentrated HCl (5 mL) was added to a solution of *N*-(2-azido-4,6-dinitrobenzylidene)-4-(*N*′,*N*′-dimethylamino)aniline *N*-oxide **5** (0.5 g) (see Refs 14, 15) in toluene (5 mL). The solution was stirred for 5—6 h, kept for

Scheme 4



* According to a previous concept,[16] a reaction of trinitrotoluene with *N*,*N*-dimethyl-4-nitrosoaniline gives an anil. Recently,[14] it has been demonstrated that the condensation product is the corresponding anil *N*-oxide (**4**).

16 h, refluxed with stirring for 2 h, and cooled. Another portion of toluene (5 mL) was added and the organic phase was separated and washed with water (5×10 mL) in a separatory funnel. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The yield of compound **2** was 76%, m.p. 124—125 °C. ^{1}H NMR (DMSO-d_6), δ: 10.61 (s, 1 H); 9.37 (s, 1 H); 8.62 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 160.68, 154.97, 148.75, 140.91, 120.61, 117.36, 111.48. MS, *m/z*: $[M]^+ = 209$, $[M+1]^+ = 210$. Found (%): C, 41.05; H, 1.75; N, 19.51. $C_7H_3N_3O_5$. Calculated (%): C, 40.20; H, 1.45; N, 20.09.

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