



SELECTIVE SYNTHESIS OF *p*-NITROSOANILINE BY THE REACTION OF UREA WITH NITROBENZENE

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P. S. Griбанov,^a M. A. Topchiy,^b L. I. Minaeva,^a G. K. Sterligov,^b
A. A. Ageshina,^b S. A. Rzhhevskiy,^b M. S. Nechaev,^b
S. N. Osipov,^a and A. F. Asachenko^{*a,b}

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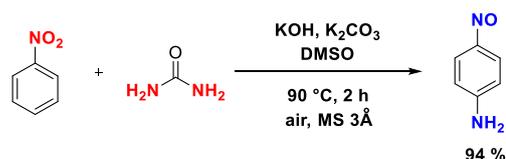
^a Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
ul. Vavilova 28, Moscow, 119991 Russia

^b Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences,
Leninskii pr. 29, Moscow, 119991 Russia

Abstract

A new efficient method for the synthesis of *p*-nitrosoaniline based on the reaction of urea with nitrobenzene is developed. Compared to the previously explored synthetic approaches, this method offers a number of significant advantages, such as the absence of hazardous wastes, almost a quantitative yield, high selectivity, and cheap reagents. Resulting *p*-nitrosoaniline serves as a key precursor for the synthesis of industrially important *p*-phenylenediamine.

Key words: *p*-nitrosoaniline, *p*-phenylenediamine, vicarious substitution, selectivity, aerobic conditions.



Introduction

p-Phenylenediamine amounts to one of the most large-scale products all over the world, with the total production of several million tons per year [1]. Its main industrial application is the synthesis of *kevlar*. *p*-Phenylenediamine is also widely used in different fields of industry: as a starting compound for the production of cosmetics, various antioxidants, fuel additives, dyes, in the synthesis of phenylene diisocyanate (a precursor for polyurethane), and for the preparation of *aramid* functional fibers which possess extremely high strength, chemical and thermal resistance. Therefore, a search for more efficient method for the synthesis of *p*-phenylenediamine, both from the economic and ecological points of view, is one of the most pressing challenges of industrial chemistry.

In turn, *p*-nitrosoaniline is a readily available compound which is used in the synthesis of different dyes [2]. The most promising field of its application is the synthesis of *p*-phenylenediamine *via* hydrogenation [3], provided the development of economically efficient method for the synthesis of *p*-nitrosoaniline.

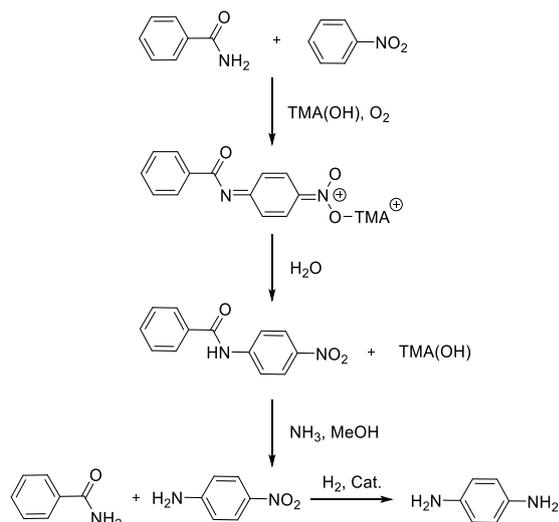
The known method for the production of *p*-nitrosoaniline is the synthesis of *N*-nitrosoaniline from aniline and sodium nitrite followed by the Fischer–Hepp rearrangement [4, 5]. The drawbacks of this method include the release of nitroso-containing compounds, environmentally hazardous waste products, and the labor-intensive synthetic procedure. Another approach to the production of *p*-nitrosoaniline [5] is two-step modification of phenol, which consists in its nitrosation at the first step followed by the interaction of resulting nitrosophenol with ammonia derivatives. Despite the detailed study using various nitrosating agents and reaction conditions, this methodology does not afford high yields of the target product (70–80%); therefore, it cannot be used in industry.

In search for new synthetic routes that would allow avoiding the above-mentioned problems, many research efforts focused on the nucleophilic aromatic substitution of hydrogen (S_N^H), which enables substantial reduction of the waste products (up to 90%) and affords aromatic amines without recourse to environmentally hazardous halogen-substituted starting compounds or intermediates [6].

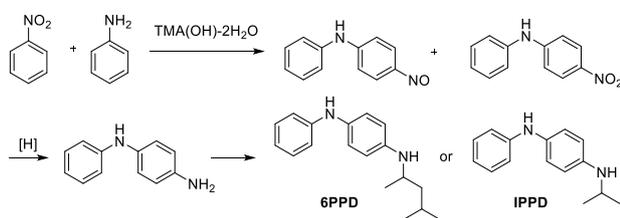
One of the first reports which entailed the implementation of S_N^H reactions in industry appeared to be a seminal paper of Michael Stern in 1993 [7], which describes the formation of aromatic amide bonds in reactions of benzamide with nitrobenzene under aerobic conditions in the presence of a base, namely, tetramethylammonium hydroxide TMA(OH). The two-step process (Scheme 1) results in a stable intermediate, *N*-(*p*-nitrophenyl)benzamide, which decomposes under the action of ammonia to benzamide and *p*-nitroaniline. The latter can be reduced subsequently to *p*-phenylenediamine.

The known industrial example of S_N^H reactions is the production of a mixture of *p*-nitrosodiphenylamine and *p*-nitrodiphenylamine by the interaction of aniline with nitrobenzene under mild conditions in the presence of TMA(OH) (Scheme 2) [8]. The subsequent hydrogenation and reductive alkylation convert this mixture to *p*-aminodiphenylamine (ADPA) as well as *N*-(1,3-dimethylbutyl)-*N'*-phenyl-*p*-phenylenediamine (6PPD) and *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD) (large-scale industrial antioxidants) [9].

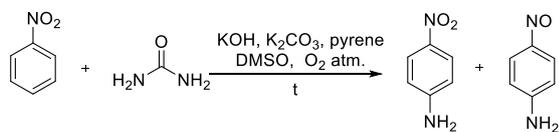
The modification of Stern's method was described in patent [2] in 2001 (the yield of *p*-nitrosoaniline was 87%) and reproduced later under laboratory conditions (with the yield of *p*-nitrosoaniline of 78%) [10, 11] (Scheme 3). This methodology consists in the use of vicarious substitution of nitrobenzene with carbamides in a polar organic solvent in the presence of a base and upon heating in an oxygen atmosphere.



Scheme 1. Synthesis of *p*-phenylenediamine from benzamide and nitrobenzene.



Scheme 2. Example of the industrially implemented S_N^H reactions.



Scheme 3. Synthesis of *p*-nitrosoaniline via vicarious substitution of nitrobenzene with carbamides.

This approach offers a number of advantages over the previously described methods. In particular, it does not require the use of expensive, toxic and poorly regenerated reagents, such as TMA(OH) [12–14]. It also does not afford low yields and does not result in side products, such as *o*-nitroaniline and *o*-nitrosoaniline, which allows for the synthesis of highly pure *p*-phenylenediamine upon further hydrogenation. However, the reaction conditions suggested by the authors have certain drawbacks. First of all, this is the use of pure oxygen atmosphere, which cannot be adapted for the industrial conditions. In this respect, the goal of the present work was to optimize the conditions of vicarious substitution of nitrobenzene with urea for its further potential implementation in industry.

Results and discussion

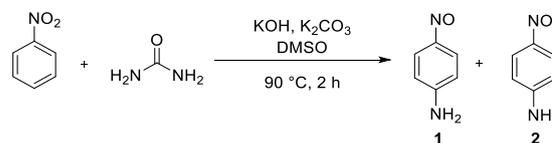
Our main task in this investigation was to optimize the process in order to enhance the yields of the products, to improve the selectivity of formation of *p*-nitrosoaniline, and to simplify the synthetic procedure from the viewpoint of potential industrial application. In an attempt to reproduce the conditions described in Ref. [2] for an aerobic atmosphere (Table 1, entry 1) [urea (60 mmol), KOH (60 mmol), K_2CO_3 (1.5 g), DMSO (25

g), nitrobenzene (2.48 g, 20 mmol) in DMSO (5 g), 90 °C, an aerobic atmosphere, 2 h], we obtained a mixture of *p*-nitroso- and *p*-nitroaniline in 3.5:1 ratio with the relatively low yield of 81%. Let us note that all subsequent vicarious substitutions were performed only in an aerobic atmosphere, unlike the cited work in which almost all the syntheses were carried out in an atmosphere of neat oxygen. Furthermore, we also did not use pyrene. We decided to evaluate the effect of the rate of addition of starting nitrobenzene on the process (Table 1, entries 2, 3) (since the rapid addition leads to substantial heating of the mixture, whereas its temperature must be kept in the range of 90 ± 4 °C).

Furthermore, we performed also the experiments in an argon atmosphere (Table 1, entry 4) and using air bubbling through the reaction mixture (Table 1, entry 5). The highest total yield of the products observed in these experiments composed 81% (Table 1, entry 1).

A literature survey revealed that the amount of water in the reaction medium strongly affects the product yield in this type of reactions [7, 8]. Therefore, the following step was to evaluate the effect of water in the reaction mixture on the course of synthesis in order to optimize the conditions and composition of the reactants. A series of the experiments were aimed to vary the amount of water or utilized molecular sieves (MS 3Å). It was found that an increase in the water content adversely affects the process, leading to an essential reduction in the product yields (Table 2). The highest efficiency was achieved at the maximum removal of water from the reaction mixture.

Table 1. Screening of conditions for the synthesis of *p*-nitrosoaniline^a



Entry	Variable parameter	Yield (%)		
		1	2	total
1	Time of nitrobenzene addition 5–10 min	63	18	81
2	Time of nitrobenzene addition 50 min	65	8	73
3	Time of nitrobenzene addition 2.5 h	49	2	51
4	Argon	48	20	68
5	Air bubbling through the reaction mixture	53	22	75

^a Reaction conditions: nitrobenzene (20 mmol, 2.48 g), urea (3.60 g, 3 eqs.), KOH (3.96 g), K_2CO_3 (1.5 g), DMSO (30 g), 90 °C, 2 h.

Table 2. Effect of the presence of water in the reaction mixture on the synthesis of *p*-nitrosoaniline^a

Entry	Water amount (mmol)	Yield (%)		
		1	2	total
1	20	57	18	75
2	40	54	13	67
3	80	55	13	68
4	100	44	12	56
5	150	35	7	42
6	MS 3Å (50 mg/mmol)	79	6	85

^a Reaction conditions: nitrobenzene (20 mmol, 2.48 g), urea (3.60 g, 3 eqs.), KOH (3.96 g), K_2CO_3 (1.5 g), DMSO (30 g), 90 °C, 2 h.

Along with the amount of water in the mixture, the reaction course (selectivity, formation of *p*-nitroso- and *p*-nitroaniline, and the total yield of the products) is significantly affected by the molar ratio of the starting reagents [8]. Table 3 presents the dependence of the total yield and process selectivity on the ratio of urea and nitrobenzene. It was shown that the use of six equivalents of urea affords the total product yield close to the quantitative one (Table 3, entry 4) and predominantly furnishes *p*-nitrosoaniline (yield 94%).

Other solvents (NMP, DMF, or PEG-600; Table 4) did not provide the results achieved with DMSO. Moreover, in the case of PEG-600, the formation of azoxybenzene (**3**) in the high yield (84%) was observed.

Table 3. Effect of the urea/nitrobenzene ratio on the synthesis of *p*-nitrosoaniline^a

Entry	Urea equivalents relative to nitrobenzene	Yield (%)		
		1	2	total
1	1	16	9	25
2	3	79	6	85
3	4	75	15	90
4	6	94	5	>99

^a Reaction conditions: nitrobenzene (20 mmol, 2.48 g), urea, KOH (3.96 g), K₂CO₃ (3.0 g), DMSO (30 g), MS 3 Å (1 g), 90 °C, 2 h.

Table 4. Screening of solvents for the synthesis of *p*-nitrosoaniline^a

Entry	Solvent	Yield (%)			
		1	2	1 + 2	3
1	DMSO	94	5	99	0
2	NMP	16	3	19	0
3	DMF	0	0	0	0
4	PEG-600	0	0	0	84

^a Reaction conditions: nitrobenzene (20 mmol, 2.48 g), urea (6 eqs.), KOH (3.96 g), K₂CO₃ (3.0 g), solvent (30 g), MS 3 Å (1 g), 90 °C, 2 h.

Experimental

General remarks

The ¹H and ¹³C NMR spectra were registered on a Bruker Avance 600 spectrometer (600 MHz ¹H, 151 MHz ¹³C). The chemical shifts were measured in parts per million (ppm) relative to the solvent signals (¹H: (CD₃)₂SO = 2.50 ppm; ¹³C: (CD₃)₂SO = 39.5 ppm) and calculated to the δ scale using the standard formulae. The reaction course and the purity of chemical compounds were controlled by TLC (silica gel 60, F254, aluminum plates); the chromatograms were visualized under UV light (254 nm). The preparative column chromatography was performed using silica gel 60 (230–400 mesh, Merck). All the solvents were purified by standard procedures.

Syntheses

A three-neck flask equipped with a magnetic stir bar, backflow condenser with a calcium chloride tube, and a thermometer was charged with urea (7.2 g), potassium carbonate (3.0 g), potassium hydroxide (3.96 g), MS 3 Å (50 mg/mmol), and DMSO (25 g). The resulting mixture was heated to 90 °C. Then, a solution of nitrobenzene (2.48 g, 20 mmol) in DMSO (5 g) was added dropwise for 5–10 min, keeping the temperature of

the reaction mixture within 90 ± 4 °C. The reaction mixture was stirred at this temperature for 2 h, then cooled and poured into water. The target products were extracted with ethyl acetate. The organic phase was separated, dried over anhydrous Na₂SO₄, and evaporated under vacuum to give a mixture of *p*-nitrosoaniline and *p*-nitroaniline as a dark-yellow solid. The purification by column chromatography (eluent: hexane/EtOAc = 5:1) afforded neat *p*-nitrosoaniline as a yellow solid. The yields of the products (*p*-nitrosoaniline and *p*-nitroaniline) at different reaction conditions were determined by the quantitative ¹H NMR analysis of the residue obtained after evaporation of the mixture by adding ferrocene as an internal standard to the resulting sample.

***p*-Nitrosoaniline** [15, 16] was obtained as a yellow solid by the previously reported procedure using the ratio of the reagents mentioned in Table 3 (entry 4). Yield: 94%. Mp: 171–172 °C (cf. with 172 °C in Ref. [15]). ¹H NMR (600 MHz, (CD₃)₂SO): δ 7.27 (s, 2H), 6.65 (s, 2H) ppm. ¹³C{¹H} NMR (151 MHz, (CD₃)₂SO): δ 163.5, 157.6, 142.2, 112.4 ppm. MS (EI) m/z: 122 (M+).

Conclusions

To summarize the results presented, we succeeded in development of a convenient, efficient and highly selective method for the synthesis of *p*-nitrosoaniline, which serves as a key precursor in the production of industrially important *p*-phenylenediamine. The suggested method consists in the vicarious substitution of nitrobenzene with urea under aerobic conditions in the presence of KOH and K₂CO₃ using dimethylsulfoxide as a solvent. Compared to the previously reported synthetic methodologies, this approach offers a number of significant advantages which include: the lack of an unstable and toxic base, namely, TMA(OH), absence of hazardous wastes, high selectivity relative to *p*-nitrosoaniline, almost quantitative total yield of the target product, use of cheap starting materials (urea, KOH, etc.), simplicity of the process performance, and essentially reduced reaction times.

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Corresponding author

* E-mail: aasachenko@ips.ac.ru. Tel: +7 (499)-647-59-27 (A. F. Asachenko)

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