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Mendeleev Commun., 2016, 26, 555–557

Mendeleev Communications

Preparation of *N*-phenyl-*p*-phenylenediamine by coupling of aniline and nitrobenzene in KOH–poly(ethylene glycol) medium

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A novel protocol for efficient coupling of nitrobenzene and aniline in poly(ethylene glycol) medium in the presence of KOH giving diphenylamine derivatives has been developed, to enable the exclusion of the toxic tetramethylammonium hydroxide catalyst commonly used in the rubber antidegradant industry.

The antidegradants are protective agents used to stabilize polymeric materials and provide aging resistance. Among them, amines are the largest class of chemicals used as antioxidants and antiozonants. The antiozonants are particularly important for protection of industrial diene rubbers. Their high level of unsaturation makes them vulnerable to ozone attack.¹ The substituted *p*-phenylenediamine (PPD) antioxidants with antiozonant effect, *N*-isopropyl-*N*'-phenyl-*p*-phenylenediamine (IPPD) and *N*-(1,3-dimethylbutyl)-*N*'-phenyl-*p*-phenylenediamine (6PPD), are among the most effective and widely used antidegradants.[†] In industry, both IPPD and 6PPD are obtained starting from *p*-nitroso-diphenylamine 1 and/or *p*-nitrodiphenylamine 2 which are reduced to *p*-aminodiphenylamine (*N*-phenyl-*p*-phenylenediamine) 3.

Chronologically one of the first industrial processes for producing the C-nitroso derivative 1, involves N-nitrosation of diphenylamine followed by Fischer-Hepp rearrangement.² The employment of carcinogenic N-nitroso derivative makes this approach safety inappropriate. The alternative Lanxess process uses a copper-catalyzed Ullmann coupling of 4-chloronitrobenzene and aniline giving nitro compound 2 in quantitative yield.³ However, the use of halogenated organics in this process generates undesirable waste stream. Direct reaction of nitrobenzene with an excess of aniline promoted by tetramethylammonium hydroxide (TMAH) at 50 °C according to the Solutia technology produces a mixture of 1 and 2 in 97% yield (Scheme 1).⁴ Both from economical and ecological points of view this approach looks the most promising.[‡] However, TMAH is a relatively expensive and toxic material, not thermally stable and cannot be fully recovered after the reaction is complete.





Scheme 1

Keeping in mind that nitrobenzene and aniline are raw materials of choice for manufacturing of key compounds **1** and **2**, we decided to focus our efforts on the optimization of the Solutia process in order to replace TMAH with less expensive and hazardous base system. A brief analysis of the available literature reflects active ongoing research to improve the catalyst/base and process itself.⁴ A variety of phase-transfer catalysts (PTC) has been tested, including, *e.g.*, tetraalkyl(aryl)ammonium salts, betaines, crown ethers, and cryptands.^{5,6} Among the systems already tested only crown ethers and cryptands in combination with an inorganic base showed comparable or better efficiency than TMAH. However, a high cost of such systems and the involved environmental issues undermine the industrial interest in their application.

In this report, binary systems consisting of poly(ethylene glycol) (PEG) and an inorganic base are suggested as a possible alternative for TMAH for the coupling of aniline and nitrobenzene. The main idea was to use PEG as high molecular weight medium possessing strong complexation ability towards alkali metal cations.⁷ Being chemically similar to crown-ethers, PEGs are available on industrial scale, cheap and nontoxic.⁸ Indeed, a brief screening of binary systems consisting of KOH powder and various PEGs under the conditions of the original Solutia process⁶ showed (Figure 1) that PEG with $M_w = 2000$ and higher worked very well giving a mixture of compounds 1 and 2 in 96–97% yields, similar to the yields achieved by the Solutia

[†] In 2011, 325 thousand metric tons of all amine-type antioxidants were consumed worldwide with IPPD and 6PPD are estimated to account for more than 50% of the market (Web: www.inchem.org).

[‡] The economical benefits of this technology are proved by the current market situation: the quota of 4-ADPA manufacturing by this method has been increasing at the expense of the other two technologies mentioned. In particular, the exclusive Russian producer of 4-ADPA by the nitrosation method had to close its factory at Kemerovo in the beginning of 2000th.



Figure 1 Dependence of yield of mixture 1 and 2 on M_w of PEG. Reaction conditions: PhNH₂ (60 ml), PhNO₂ (8.85 g), KOH (5.9 g), PEG (50 ml), air (60 mbar), 60 °C, 2.5 h.

industrial process, and higher than that in the best laboratory protocol using TMAH base (93%).^{5,9}

We have observed that a slow addition of nitrobenzene to a solution of potassium hydroxide in a mixture of PEG 4000 containing an excess of aniline under aerobic conditions immediately resulted in red coloration of the reaction mixture. Analysis of the final (2.5 h, 60 °C) reaction mixture by HPLC showed that products **1** and **2** were formed in 76 and 20% yields, respectively (Scheme 1).[§] An additional advantage of this method is an apparently higher selectivity, as azobenzene and phenazine, common by-products of the TMAH method, were formed only in trace amounts not exceeding 0.9%.

Both the amount of PEG and the nature of inorganic base have been shown to play a critical role for achieving high selectivity and performance.[¶] The optimal loading of PEG was found to be 0.36 g per mmol of KOH, which is equivalent to *ca*. 8.3 oxygen atoms (oxyethylene units of PEG) per one K⁺, close to common coordination environment of the potassium cation.^{10,11}

The effect of alkali metal cation is outlined in Table 1. The results clearly show that the system NaOH–PEG 4000 gave very low yields of the target products.^{††} We assume that the dramatic difference between potassium and sodium hydroxides in the coupling reaction can be explained by ability of the PEGs to more strongly bind potassium cation in comparison with sodium ion, resulting in increased basicity and reactivity of OH⁻ in KOH–PEG.¹³ The higher stability of potassium complexes compared to sodium ones was established using conductivity measurements,¹⁴ calorimetric¹⁵ and matrix-assisted laser desorption ionization (MALDI) measurements.¹⁶ For example, in terms of Gibbs free

[¶] The optimized loading of PEG is 0.55 g per mmol of nitrobenzene with PEG–KOH weight ratio 5.6.

Table 1 Effect of alkali metal cation on performance of the coupling reaction.^a

Base	PEG/Base ratio ^b	Conversion (%)	Yield of $1 \ (\%)$	Yield of $2 (\%)$
NaOH	8.3	97.7	< 0.2	< 0.2
KOH	8.3	100	75.9	20.3
КОН	0	92.7	< 0.2	< 0.2

^{*a*}Reaction conditions: inorganic base (95 mmol), PhNH₂ (60 ml), PhNO₂ (8.85 g), PEG (35 or 0 g), air (60 mbar), 60 °C, 2.5 h. ^{*b*}The ratio is expressed as a number of PEG oxyethylene units per a metal atom.

energy, the potassium cation forms stronger complexes than the sodium one with respective PEGs or PEG derivatives by the value up to 1.2-1.3 kcal mol⁻¹.¹⁷

The mechanism of the main process is apparently the oxidative nucleophilic aromatic substitution of hydride,^{‡‡} most probably involving the formation of anionic σ -complex **4**, which cannot give the respective substitution product directly as the cleavage of hydride-ion cannot take place. Instead, the intermediate complex is oxidized and aromatized either by dioxygen or nitro group (Scheme 2), which accounts for the formation of reduced by-products, such as nitroso derivatives or phenazine. In fact, the predominate formation of nitroso derivative **1**, while **2** is a minor product, reveals that nitro group, rather than air dioxygen, is the main operative oxidant. Such a mechanism was considered for similar reactions in the presence of TMAH and Bu^tOK·(18-crown-6) bases.^{6,8}



When similar reactions are performed under anaerobic conditions, azobenzene is often formed as the reduced by-product.¹⁸ In our case, aerobic conditions dramatically decrease the formation of such useless by-products.

The lower amount of phenazine observed for KOH–PEG binary system compared to TMAH is difficult to explain in this stage of investigation. This by-product is likely to be formed *via ortho*-attack of the anilide anion on nitrobenzene followed by intramolecular oxidation and ring closure of the formed *ortho*-substituted σ -complex. One possible explanation of the observed phenomenon originates from a larger sterical hindrance of the anilide anion in tight ion pair [PhNH][K·PEG] that makes such a pathway less favorable.

The 1 + 2 mixture can be easily converted to **3** in almost quantitative yield by catalytic hydrogenation (see Scheme 1).¹⁹ The hydrogenation catalyzed by 10% Pd/C can be carried out in the presence of PEG directly in the reaction mixture formed after the coupling of nitrobenzene and aniline. Further, PEG can be recovered from the residue left after isolation of **3** by vacuum distillation, and can be further reused for the coupling of the next portions of aniline and nitrobenzene several times.

[§] General procedure for reaction of nitrobenzene and aniline. A 250 ml reactor with a mechanical stirrer was charged with PEG 4000 (35 g) and potassium hydroxide (5.88 g, 95 mmol). For dissolving of KOH small amount of methanol (3 ml) was added and the mixture was heated to 120 °C under vigorous stirring for 20 min. The clean homogenous solution obtained was cooled to 60 °C, and aniline (60 ml, 0.65 mol) was added in one portion. Then the reactor was connected to vacuum line, and under pressure of 60 mbar dry air was bubbled through the reaction mixture at flow rate 375 ml min⁻¹, and the air flow was kept at this rate until the reaction was complete. Using a syringe pump nitrobenzene (8.85 g, 72 mmol) was introduced at the rate 0.1 ml min⁻¹ keeping the temperature at 60 °C. After additional 1 h excess of aniline was removed by distillation under 0.1 mbar pressure, and the residue was neutralized with HCl solution (10 N, 10.5 ml) to give a solution of (4-nitrosophenyl)phenylamine (10.83 g, 76%) and (4-nitrophenyl)phenylamine (3.85 g, 20%) in PEG 4000/ water. For next manipulations and details, see Online Supplementary Materials.

^{††} Also the KOH–PEG system (instead of early used NaOH/15-crown-5)¹² was found to allow the convenient synthesis of bis(indenyl)methanes starting from indenes and ketones to be performed, *e.g.*, acetone and indene give 2,2'-bis(1-indenyl)propane in one step in 55% yield. Analogously to the coupling of aniline and nitrobenzene, the application of NaOH does not afford the target bis(indenyl)methanes.

^{‡‡} The radical mechanism cannot be fully excluded because the admixture of 4-ADPA was detected in the reaction mixture after coupling with PEG–KOH. The amount of 4-ADPA for PEG 4000 was less than 0.4%, whereas in case of PEG 300 and 400 it was up to 3.6%.

In summary, a convenient protocol for the synthesis of 4-aminodiphenylamine which is a key half-product for important rubber antidegradants has been developed. This protocol involves the reaction of nitrobenzene with aniline under aerobic conditions using KOH–PEG medium followed by Pd/C-catalyzed hydrogenation of the coupling products by molecular hydrogen. This approach may have significant commercial implications, since it avoids the use of TMAH. The observed low yield of undesired byproducts and the feasibility to reuse of PEG are another advantage of this approach. In other words, the applied binary system, KOH–PEG, can be considered as nontoxic, stable, inexpensive alternative for TMAH in this important industrial process.

This work was supported by the Ministry of Education and Science of the Russian Federation (agreement no. 14.613.21.0041, the project unique identifier RFMEFI61315X0041).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.11.033.

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Received: 22nd July 2016; Com. 16/5002