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Reductive Activation of Arenes: XVI.* Anionic Products from Reduction of *p*-Tolunitrile with Sodium in Liquid Ammonia and Their Reaction with Butyl Bromide

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Abstract—Study of oxidation, protonation, and alkylation of the products obtained by one- and two-electron reduction of *p*-tolunitrile with sodium in liquid ammonia showed that these products are, respectively, *p*-tolunitrile radical anion and 1-cyano-4-methyl-2,5-cyclohexadienyl anion. The latter is formed by protonation of *p*-tolunitrile dianion with ammonia. The two-electron reduction involves protonation of *p*-tolunitrile dianion with initial *p*-tolunitrile, which gives rise to 4-cyanobenzyl anion. The yield of the latter depends on the order of mixing of the reactants. The anionic reduction products react with butyl bromide to afford products corresponding to *ipso* alkylation with respect to the cyano group, 4-butyltoluene and 3-butyl-3-cyano-6-methyl-1,4-cyclohexadiene, as well as the alkylation product at the benzylic position, 4-pentylbenzonitrile. The formation of 4-butyltoluene indicates the possibility for selective synthesis of *p*-alkyltoluenes by reductive alkylation of *p*-tolunitrile.

In the framework of our works on the effect of structural factors on the regioselectivity and mechanism of alkylation of anionic species formed by reduction of aromatic cyano compounds, we started a study of the influence of electron-donor substituents in going from benzonitrile to *m*-tolunitrile (see [1] and references therein). We found that one- and two-electron reduction of *m*-tolunitrile with sodium in liquid ammonia gives, respectively, the corresponding radical anion and 1-cyano-3-methyl-2,5-cyclohexadienyl anion as a result of protonation of *m*-tolunitrile dianion with ammonia. These anionic species reacted with alkyl halides according to the *ipso*-addition pattern to afford the corresponding *m*-alkyltoluene and 3-alkyl-3-cyano-5-methyl-1,4-cyclohexadiene. The exceptional *ipso* selectivity in the alkylation of the above anionic species, which is consistent with localization of the maximal negative charge and is observed regardless of the alkyl halide structure, as well as the absence of products in the reaction with *tert*-butyl bromide, suggests that the process follows

the S_N mechanism. Thus, both the nature of one- and two-electron reduction products derived from benzonitrile [2, 3] and *m*-tolunitrile [1] in liquid ammonia and their reactivities toward alkyl halides are similar. This means that methyl substitution of the *meta* position does not affect the properties of the reduced forms. Our results differ from published data for *m*-tolunitrile radical anion generated electrochemically in DMF, according to which this species exhibits not only nucleophilic but also electron-donor properties with respect to alkyl halides [4]. A reason for the observed disagreement may be considerably lower (than in [4]) reaction temperature which favors S_N rather than electron-transfer mechanism [5]. In keeping with the data of [4], the ability of the radical anions to act as one-electron reducing agent increases in going from *m*-tolunitrile to *p*-tolunitrile. The greater effect of the *para*-methyl group on the ability of radical anion to react according to one or another mechanism is consistent with the structure of the highest occupied molecular orbital (HOMO) of benzonitrile radical anion [6]: the electron density in the *para* position with respect to the cyano group is higher than in the *meta* position.

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* For communication XV, see [1].

The above data prompted us to perform an experimental study of the effect of methyl group in the *para* position on the mechanism of reaction of reduced forms of cyanobenzenes with alkylating agents. As a first step in this direction, the goal of the present work was to examine the nature of anionic species formed by one- and two-electron reduction of *p*-tolunitrile (**I**) with sodium in liquid ammonia and study their alkylation.

The reduced forms of nitrile **I** were generated by the known method [1] implying the action of 1 or 2 equiv of metallic sodium on a solution or suspension of the substrate in liquid ammonia at –33°C. As shown in [1], the radical anion formed by one-electron reduction of *m*-tolunitrile with sodium in liquid ammonia does not undergo any irreversible transformations, so that the initial compound is readily regenerated by oxidation of the reduced form. The product of two-electron reduction, *m*-tolunitrile dianion, is protonated with ammonia to give 1-cyano-3-methyl-2,5-cyclohexadienyl anion. In the case of *p*-tolunitrile, the process may be complicated due to high acidity of the methyl C–H bonds ($pK_a \approx 30.8$, DMSO, 25°C [7]); therefore, the substrate can compete with ammonia ($pK_a \approx 34$, –33°C [8]) for anionic reduced forms. The high acidity of the substrate may also be responsible for instability of the radical anion. According to Rieger *et al.* [9], the ESR spectrum of *p*-tolunitrile radical anion disappears within a short period. Chemical testing of the nature of the anionic reduction products showed the following. Nitrile **I** was subjected to one-electron reduction (to prevent two-electron reduction, the substrate was taken in a 10% excess), and the reduction product was kept for 30 min and oxidized with oxygen to obtain 80% of initial nitrile **I** and an insignificat amount of *p*-toluamide. The latter is likely to be formed by hydrolysis of the substrate. These data indicate a relatively high stability of *p*-tolunitrile radical anion (**II**) under the given conditions. Two-electron reduction of **I** was effected with the use of ~2.2 equiv of sodium to ensure complete process. The subsequent treatment with oxygen, as in the case of *m*-tolunitrile [1], gave no initial compound. After evaporation of ammonia, the reaction mixture was diluted with water and extracted with ether to isolate 8% of *p*-toluamide and 6% of *p*-cresol. Treatment of the two-electron reduction products with water gave nitrile **I** and *p*-cresol in 75 and 12% yield, respectively. Taking into account our previous data [1, 3], we believe that *p*-tolunitrile dianion generated by the action of sodium in liquid ammonia undergoes protonation to give 1-cyano-4-methyl-2,5-cyclohexadienyl anion (**III**). The oxidation

of anion **III** is likely to involve intermediate formation of methylcyclohexadienone [10], and it gives rise to *p*-cresol and compounds which are not extracted from aqueous solution. Probably, these are products of decomposition of the benzene ring and/or polymers. Obviously, protonation of anion **III** leads to 3-cyano-6-methyl-1,4-cyclohexadiene which is converted into initial nitrile **I** upon treatment of the reaction mixture. The composition of products obtained by quenching of the reduced forms with water does not allow us to judge whether *p*-cyanobenzyl anion is formed from **I** as a result of protonation of anionic species. However, we expected that the necessary information can be derived from the structure of products obtained by alkylation of the reduced forms.

Thus, the above data together with available information on the reduction of aromatic nitriles in liquid ammonia [1–3] and electrochemical reduction of *p*-tolunitrile (**I**) [4] suggest that one- and two-electron reduction of **I** in liquid ammonia leads to formation of radical anion **II** and anion **III**, respectively. These anionic species are sufficiently stable to examine their reactivity with respect to alkyl halides.

The alkylation of the reduced forms of nitrile **I** was carried out by adding butyl bromide to their solution in liquid ammonia at –33°C. The resulting mixtures were analyzed by ^{1}H NMR, GLC, and GC–MS. The amounts of the reactants and product composition are given in table. Spectral parameters of the products are given in Experimental. We have found that one- and two-electron reduction products obtained from nitrile **I** by the action of sodium in liquid ammonia react with butyl bromide to give 4-butyltoluene (**IV**), 3-butyl-3-cyano-6-methyl-1,4-cyclohexadiene (**V**), and 4-pentylbenzonitrile (**VI**) (run nos. 1, 4). Nitrile **VI** was identified by GLC using an authentic sample. Nitrile **V** was synthesized for the first time. 4-Butyltoluene (**IV**) was reported previously (see, e.g., [11]); however, there are no published spectral data sufficient for its identification. Therefore, the products were isolated by chromatography from the reaction mixtures, and their structure was confirmed by spectral methods. The ^{1}H NMR spectrum of **IV** contains a singlet from the methyl group attached to the aromatic ring (δ 2.31 ppm), a triplet from the butyl α-CH$_2$ protons (nearest to the benzene ring; δ 2.56 ppm), and unresolved signals from the remaining seven protons of the butyl group at δ 0.91, 1.32, and 1.58 ppm. In the aromatic region we observed a singlet at δ 7.07 ppm, typical of 1,4-dialkylbenzenes [12]. The ^{1}H signals of nitrile **V** were assigned by analogy with 3-cyano-3-butyl-1,4-cyclohexadiene [2] and 1-butyl-1-cyano-4-methyl-1,4-di-

Reaction of reduced forms of nitrile **I** with butyl bromide

Run no.	Amounts of reactants, mmol			Composition of product mixtures, mmol (GLC data)[a]			
	nitrile **I**	sodium	BuBr	nitrile **I**	butyltoluene **IV**	nitrile **V**	nitrile **VI**
1	3.3	3.0	3.0	0.79	0.36	0.81	0.86
2[b]	3.1	3.0	3.0	0.82	0.29	0.70	0.77
3[c]	3.1	3.0	3.0	0.67	0.30	0.89	0.83
4	3.0	6.5	5.0	0.10	1.10	0.70	0.50
5[d]	3.0	6.5	3.0	0.10	1.82	0.81	0.08

[a] Average data from 2–3 parallel runs are given.
[b] The ammonia solution containing reduction products was kept for 2.5 h at –33°C.
[c] At –65°C.
[d] The reduction was carried out by method *b*.

hydronaphthalene [3]. The spectrum contains three groups of signals in the region δ 0.92–1.70 ppm (overall intensity 9H), which belong to the butyl fragment, a multiplet at δ 2.70 ppm (6-H), and a doublet of doublets at δ 5.86 ppm (J = 10, 3.5 Hz) from protons on C^1 and C^5. Insofar as diene **V** is formed as a mixture of two stereoisomers with *cis* and *trans* arrangement of the alkyl sybstituents on C^3 and C^6, protons of the methyl group on C^6 appear as two doublets at δ 1.12 and 1.16 ppm). For the same reason, protons on C^2 and C^4 give two doublets of doublets at δ 5.56 and 5.59 ppm (J = 2 Hz). The high-resolution mass spectrum of nitrile **V** is consistent with the assumed structure.

The overall yield of the alkylation products obtained from doubly reduced nitrile **I** (~77%) is typical of reactions involving two-electron reduction products [1, 3]. Contrastingly, the overall yield of compounds **IV**–**VI** obtained from the one-electron reduction product (~70%) exceeds the theoretical value calculated on the basis of stoichiometry of radical anion

reactions (50%). The ratio of nitriles **V** and **VI** in run no. 1 is approximately equal to unity. Taking into account these data and the schemes describing reductive alkylation of benzonitrile and *m*-tolunitrile [1–3], we can propose the following paths for formation of compounds **IV**–**VI** in the processes under study. *p*-Tolunitrile radical anion (**II**), as well as radical anions derived from benzonitrile and *m*-tolunitrile, is alkylated at the *ipso* position with respect to the cyano group to give anion **VII**. The latter can undergo transformations along two pathways. The first of these is decyanation leading to butyltoluene **IV**, and the second is protonation to afford nitrile **V** (Scheme 1). Here, the protonating agent may be initial nitrile **I** which is present in excess and is regenerated upon formation of anion **VII**. The resulting cyano-benzyl anion **VIII** reacts with butyl bromide to give nitrile **VI**. An alternative pathway to compound **VI** implies formation of cyanobenzyl anion **VIII** directly from radical anion **II**. As we already noted, radical anion **II** generated electrochemically in DMF was

Scheme 1.
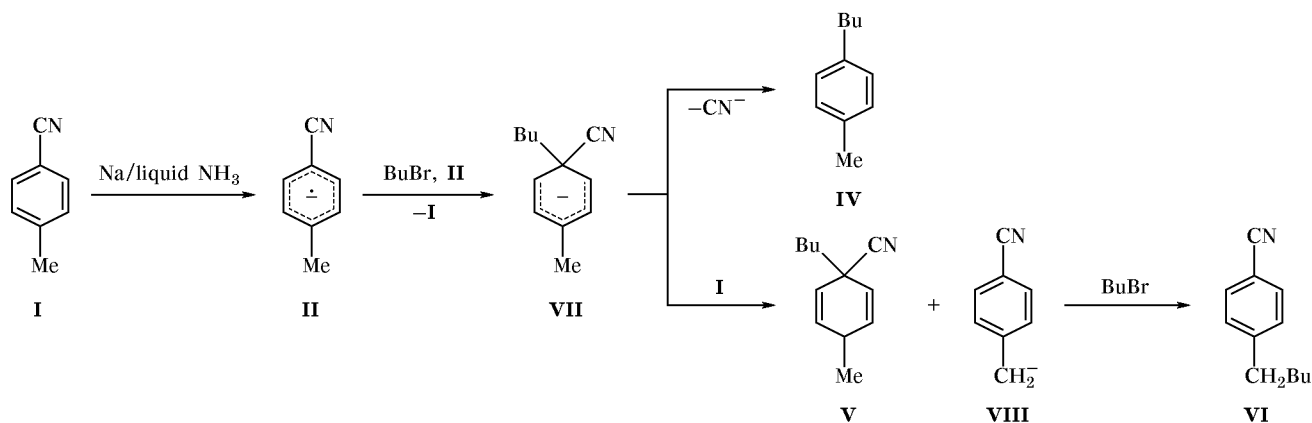
Scheme 2.
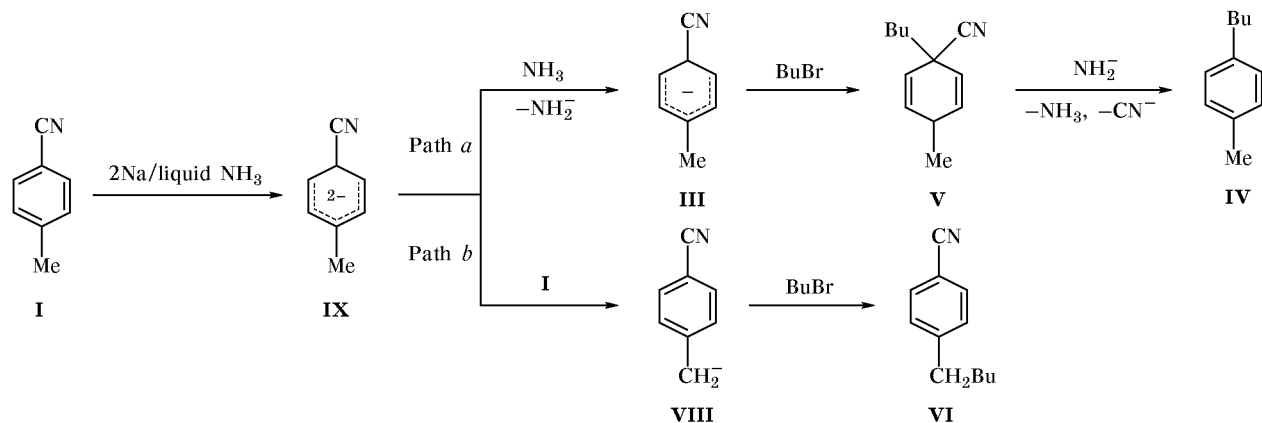
shown to be unstable [9]. In order to verify the possibility for the alternative pathway, the product of one-electron reduction of nitrile **I** was subjected to alkylation in two ways: (1) a solution containing the reduced form was preliminarily kept for 2.5 h at –33°C and (2) butyl bromide was quickly added to the reduced form generated at –60 to –65°C. In both cases, the ratios of the alkylation products were almost similar (cf. runs nos. 2 and 3). Therefore, we presume that radical anion **II** generated by the action of sodium on nitrile **I** in liquid ammonia is stable in the absence of electrophiles and that the most probable way of formation of nitrile **VI** is the transformation sequence shown in Scheme 1. Thus, the products of alkylation of radical anion **II** are compounds **IV** and **V**, and their yield is about ~40%, i.e., ~80% of the theoretical value.

Scheme 2 illustrates the alkylation of the two-electron reduction product. Protonation of *p*-tolunitrile dianion (**IX**) with ammonia gives 1-cyano-4-methyl-cyclohexadienyl anion (**III**) which is alkylated at the *ipso* position with respect to the cyano group (path *a*). The resulting diene **V** undergoes partial dehydrocyanation by the action of sodium amide, leading to butyltoluene **IV**. When the reduction is carried out with excess nitrile **I**, the substrate itself is capable of acting as proton donor toward dianion **IX** (path *b*). In this case, apart from anion **III** and the corresponding alkylation products (**IV** and **V**), cyanobenzyl anion **VIII** is obtained, and the latter reacts with butyl bromide, yielding nitrile **VI**.

The assumption that the substrate participates in protonation of the dianion was verified by changing the order of mixing of the reactants while generating the reduced form. A solution of nitrile **I** was added to a solution of sodium in liquid ammonia, so that the possibility for protonation of dianion **IX** with initial

nitrile **I** was excluded. In this case, the reaction should not take path *b*, and no anion **VIII** and hence nitrile **VI** should be obtained. As a result, we isolated only compounds **IV** and **V** (the yield of nitrile **VI** was negligible; see table, run no. 5). In going from run no. 4 to run no. 5, the ratio **IV**:**V** increased from ~1.6 to ~2.2. This is consistent with increase in the amount of amide ion which is formed according to path *a*.

Thus, unlike benzonitrile and *m*-tolunitrile, the reductive amination of *p*-tolunitrile (**I**) is accompanied by side process due to relatively high acidity of the methyl C–H bonds in the substrate. In the alkylation of the two-electron reduction product, the side process can be minimized by changing the order of mixing of the reactants. The alkylation of radical anion **II** and anion **III** occurs at the *ipso* position with respect to the cyano group. By analogy with our previous data [1, 2], this is an indirect evidence in favor of the S_N mechanism of reactions of butyl bromide with anionic species derived from nitrile **I** in liquid ammonia.

Comparison of our present results with those reported in [1] shows that the alkylbenzene-to-cyclohexadiene ratio in the products of reductive alkylation considerably decreases in going from *m*-tolunitrile to its *para*-substituted isomer. An analogous effect, which originates from reduction of the acidity of the C_{sp^3}–H bond in the initially formed dihydroarene (due to alkyl substitution at the same carbon atom) [13], was observed in the reductive alkylation of 1-naphthonitrile and 4-methylnaphthonitrile [3]. The formation of a considerable amount of nitrile **V** reduces the synthetic significance of the reaction under study as a new route to *p*-alkyltoluenes (cf. [1]). However, we have shown that nitrile **V** undergoes dehydrocyanation to butyltoluene **IV** by the action of sodium amide in liquid ammonia on a mixture of

compounds **IV** and **V** obtained in run no. 5. In this case, the yield of butyltoluene **IV** is ~70% (calculated on the initial nitrile **I**).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WP-200SY instrument from solutions in CDCl$_3$. The precise molecular weights were determined by high-resolution mass spectrometry on a Finnigan MAT-8200 mass spectrometer. The reaction mixtures were analyzed by GLC on an LKhM-7A chromatograph under the following conditions: 2.5-m $\times$ 2-mm column packed with 15% of SKTFV-83 on Chromosorb W; oven temperature programming from 100 to 300°C (10°C/min); carrier gas helium, flow rate 0.6 l/h. The products were identified by GC–MS using a Hewlett Packard G1081A setup consisting of an HP 5890 Series II gas chromatograph and an HP 5971 mass-selective detector; electron impact, 70 eV; HP-5 column, 30 m $\times$ 0.25 mm $\times$ 0.25 μm (5% of diphenyl- and 95% of dimethylsiloxane); carrier gas helium, flow rate 1 ml/min; oven temperature programming from 50°C (2 min) at 10 deg/min to 280°C (5 min); injector temperature 280°C; ion source temperature 173°C; data acquisition at 1.2 scan/s in the mass range from 30 to 650 amu.

The following reagents and solvents were used. Liquid ammonia was purified by dissolution of metallic sodium and subsequent distillation into a reciever cooled to –70°C; oxide coating was removed from metallic sodium (pure) under a layer of dry hexane; *p*-tolunitrile was synthesized from *p*-toluoyl chloride by a procedure analogous to that reported in [14], mp 27–28°C (published data [15]: mp 26–28°C); butyl bromide was passed through a layer of aluminum oxide and was then distilled, its boiling point coincided with that given in [15].

Reduction of *p*-tolunitrile (I) with sodium in liquid ammonia. *a*. A required amount of metallic sodium (see table) was added to a solution of nitrile **I** (~5 $\times$ 10^{-2} mol) in liquid ammonia under stirring at –33°C, and the mixture was kept for 10–30 min at that temperature.

b. A solution of nitrile **I** in 5 ml of anhydrous THF was added with stirring at –35°C to a solution of metallic sodium (~10^{-1} mol) in liquid ammonia, and the mixture was kept for 10 min at that temperature.

Reactions of the reduction products of *p*-tolunitrile (I) with electrophilic reagents. Oxidation. Oxygen was dried by passing through a layer of calcium chloride and was bubbled over a period of 15–20 min through a solution containing products of reduction of *p*-tolunitrile, obtained by reaction of 0.069 g (3.0 mmol) of sodium with 0.386 g (3.3 mmol) of nitrile **I** or of 0.149 g (6.5 mmol) of sodium with 0.351 g (3.0 mmol) of nitrile **I**. The mixture was stirred for 20 min, and 5 ml of methanol and 50 ml of diethyl ether were added. The mixture was stirred until the ammonia evaporated, and 50 ml of water was added. The ether layer was separated, the aqueous layer was extracted with ether (2 $\times$ 50 ml), and the combined extracts were washed with water, dried over MgSO$_4$, and evaporated. The residue was analyzed by ^{1}H NMR spectroscopy and GLC. By oxidation of the one-electron reduction product we obtained 0.34 g of a mixture containing 90% of initial nitrile **I** (yield ~80%) and 10% of *p*-toluamide. Oxidation of the two-electron reduction product gave 0.01 g of *p*-toluamide (~8%) and 0.02 g (~6%) of *p*-cresol.

Protonation of the two-electron reduction product of *p*-tolunitrile (I). Water, 0.01 mol (0.18 ml), was added dropwise with stirring to a solution of the two-electron reduction product obtained by the action of 0.149 g (6.5 mmol) of sodium on 0.351 g (3.0 mmol) of nitrile **I**. The mixture was kept for 20 min, and 50 ml of diethyl ether was added. The mixture was then treated as described above. After removal of the solvent, the residue contained 0.26 g of initial nitrile **I** (yield ~75%) and 0.04 g (12%) of *p*-cresol.

Reaction of the reduction products of *p*-tolunitrile (I) with butyl bromide. Butyl bromide was added to a solution of the reduction products prepared by method *a* (run nos. 1–4) or *b* (run no. 5) (for amounts of the reactants, see table). In run no. 2, the ammonia solution of reduction products was kept for 2.5 h at –33°C before addition of butyl bromide. In run no. 3, the reduction products were generated and butyl bromide was added at –60°C. The mixture was stirred until the ammonia evaporated by half (~0.5 h), and 50 ml of diethyl ether was added. The mixture was then treated as described above. The products were analyzed by ^{1}H NMR, GLC, and GC–MS (see table). Individual compounds were isolated by column chromatography on silica gel (40/80 μm) using hexane–diethyl ether (19:1) as eluent or by TLC using plates with a fixed layer of silica gel LSL$_{254}$ (5/40 μm) containing 13 wt % of gypsum, eluent hexane–diethyl ether (9:1). The separation process was monitored visually by irradiation of dried plates with UV light. The structure of the products was determined by ^{1}H NMR spectroscopy and high-resolution mass spectra.

4-Butyltoluene (IV). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 0.91 t (3H, CH$_3$), 1.32 m (2H, CH$_2$), 1.58 m

(2H, CH_2), 2.31 s (3H, CH_3), 2.56 t (2H, CH_2), 7.07 s (4H, 2-H, 3-H, 5-H, 6-H). Found M 148.1250. $C_{11}H_{16}$. Calculated: M 148.1251.

3-Butyl-3-cyano-6-methyl-1,4-cyclohexadiene (V) (a mixture of two stereoisomers). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 0.92 t (3H, CH_3), 1.12 d and 1.16 d (3H, CH_3), 1.22–1.48 m [4H, $(CH_2)_2$], 1.70 m (2H, CH_2), 2.70 m (1H, 6-H) 5.56 d.d and 5.59 d.d (2H, 2-H, 4-H), 5.86 d.d (2H, 1-H, 5-H). $J_{1,2} = J_{4,5} =$ 10 Hz, $J_{1,6} = J_{5,6} = 3.5$ Hz, $J_{2,6} = J_{4,6} = 2$ Hz, $J_{6,6} =$ 7 Hz. Found: M 175.1343. $C_{12}H_{17}N$. Calculated: M 175.1360.

Dehydrocyanation of nitrile V. A solution containing compounds **IV–VI** (which was obtained in run no. 5) was added to a suspension of ~8 mmol (0.300 g) of sodium amide in 40 ml of liquid ammonia. The mixture was stirred for 20 min and 10 ml of water was added. When the ammonia evaporated, the mixture was treated as described above to obtain 0.330 g of a mixture containing (according to the ^{1}H NMR and GLC data) 94% of 4-butyltoluene (**IV**) (~2.1 mmol), 2% of nitrile **V**, and 4% of nitrile **VI**.

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