Russian Journal of General Chemistry, Vol. 72, No. 8, 2002, pp. 1248–1250. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 8, 2002, pp. 1330–1332.
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Synthesis of *N*-Isobutylanilines Substituted in the Benzene Ring and Their Reactivity in Arenesulfonylation

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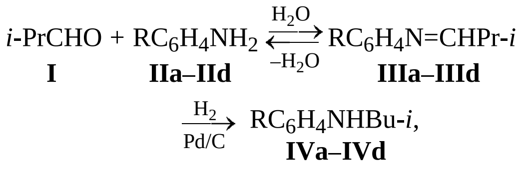
Received September 12, 2000

Abstract—Secondary aliphatic–aromatic amines were synthesized by hydrogenative amination of aliphatic aldehydes with aromatic amines. The kinetics of arylsulfonation of the resulting alkylarylamines with benzenesulfonyl chloride and its monosubstituted derivatives in 2-propanol at 298 K were studied. The activation parameters of the reaction of ring-substituted *N*-isobutylanilines with 3-nitrobenzenesulfonyl chloride were determined.

The reactivity of secondary aliphatic–aromatic amines in arenesulfonylation has not yet been studied, on account of certain difficulties in their synthesis and isolation, as well as the low rate of their reaction with aromatic sulfonyl chlorides [1]. We now possess scarce information [2] on the kinetics of acylation of *N*-methylaniline with substituted benzoyl chlorides in benzene. At the same time, sulfonyl amides obtained by reactions of N-alkylated aromatic amines with arenesulfonyl halides have found wide use as drugs, dyes, plasticizers, and in production of biologically active compounds.

We performed hydrogenative amination of 2-methylpropanal (**I**) with aniline and its derivatives **IIa**–**IId** in mild conditions (p_{H_2} 0.1 MPa, 318 K, 2-propanol) in the presence of Pd/C. This method of synthesis of alkylated amines provides a facile and versatile synthetic route to their aliphatic–aromatic representatives, since it occurs in mild conditions, requires simple equipment, and allows one to prepare secondary or tertiary amines by varying reaction conditions [3].

Hydrogenative amination of 2-methylpropanal with aniline and its derivatives comprises the following chemical reactions.



$$\underset{\mathbf{I}}{i\text{-PrCHO}} + \underset{\mathbf{IIa–IId}}{\mathrm{RC_6H_4NH_2}} \overset{H_2O}{\underset{-H_2O}{\rightleftarrows}} \underset{\mathbf{IIIa–IIId}}{\mathrm{RC_6H_4N{=}CHPr}\text{-}i}$$

$$\xrightarrow[Pd/C]{H_2} \underset{\mathbf{IVa–IVd}}{\mathrm{RC_6H_4NHBu}\text{-}i,}$$

R = H (**a**), 4-Me (**b**), 4-MeOCO (**c**), 4-EtOCO (**d**).

The process involves initial formation of azomethine **IIIa**–**IIId** and its subsequent hydrogenation to alkylarylamine **IVa**–**IVd**.

Preliminary experiments showed that in the chosen conditions hydrogenative amination of all the substrates occurs in the kinetic region and is zero-order in substrate and first-order in catalyst and hydrogen. The rate constant of hydrogenative amination of aldehyde **I** with amines **IIa**–**IId** was calculated as described in [4]. Given are azomethine no. and hydrogenation rate constant $k \times 10^5$ (l g^{-1} s^{-1}): **IIIa**, 9.2 ± 1.2; **IIIb**, 6.9 ± 0.7; **IIIc**, 26.3 ± 2.3; and **IIId**, 4.8 ± 0.3.

It is known that the rate of hydroamination of aldehydes with aniline and its derivatives depends on the nature and position of substituent in the aromatic ring of the aminative agent. As found by Klyuev *et al.* [5], the dependence of the apparent rate constant of hydrogenative amination of furfural with aromatic amines in the presence of Pd/C on classical Hammett constants is linear: The hydroamination rate increases with increasing σ. The referees explained this fact by decreasing electron density on the azomethine C=N fragment and the resulting weakening of the coordination bond between the active center of the catalyst and the reaction center of the substrate. The respective dependence for hydrogenative amination of aldehyde **I** with aromatic amines on palladium-containing catalysts (AB-17-8-Pd, etc.) is bell-shaped: The amination rate decreases with increasing σ [6]. In our case, the hydroamination rate is hardly related to the effect of substituent in the aromatic ring of the amine, since the experimental evidence obtained in insufficient for the shape of the rate–σ dependence for hydrogenative amination of aldehyde **I** with amines **IIa**–**IId** to be judjed about with assurance.

Analysis of the reaction mixtures for by-products

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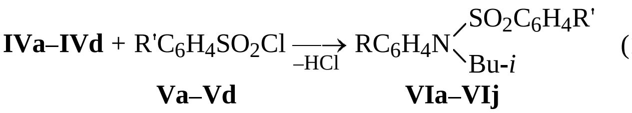
(tertiary amines) and unreacted amines **IIa**–**IId** was perfomed by GLC. The yields of target secondary amines **IVa**–**IVd** were always close to 100%.

Amines **IVa**–**IVd** were separated from the catalyst and reacted with benzenesulfonyl chloride (**V**) and its monosubstituted derivatives in 2-propanol.



$$\mathbf{IVa–IVd} + R'C_6H_4SO_2Cl \xrightarrow[-HCl]{} RC_6H_4N\begin{matrix}SO_2C_6H_4R' \\ Bu\text{-}i\end{matrix} \qquad (1)$$

Va–Vd **VIa–VIj**

V, R' = H (**a**), 4-Me (**b**), 3-NO$_2$ (**c**), 4-NO$_2$ (**d**); **VI**, R = H, R' = H (**a**), R = H, R' = 4-Me (**b**), R = H, R' = 3-NO$_2$ (**c**), R = H, R' = 4-NO$_2$ (**d**), R = 4-Me, R' = H (**e**), R = 4-Me, R' = 4-Me (**f**), R = 4-Me, R' = 3-NO$_2$ (**g**), R = 4-Me, R' = 4-NO$_2$ (**h**), R = 4-MeOCO, R' = 3-NO$_2$ (**i**), R = 4-EtOCO, R' = 3-NO$_2$ (**j**).

The kinetics of reaction (1) were studied by spectrophotometry [7] using lithium 2,6-dinitrophenolate as indicator. Preliminary experiments showed that this indicator exerts no catalytic effect.

The arenesulfonylation rate fits the second-order kinetic equation (2):

$$-dc_{\mathrm{V}}/d\tau = kc_{\mathrm{IV}}c_{\mathrm{V}}. \qquad (2)$$

Here k is the acylation rate constant and c_{IV} and c_{V} are the current concentrations of amine **IVa**–**IVd** and sulfonyl chloride **Va**–**Vd**, respectively.

The initial concentration of alkylarylamine **IVa**–**IVd** in all kinetic experiments was 10^2–10^3 times higher than the initial concentration of arenesulfonyl chloride **Va**–**Vd**, which allowed the pseudo-first-order rate constant k_1 to be calculated by the Guggenheim method and the second-order rate constants, by Eq. (3).

$$k = k_1/c^0_{\mathrm{IV}}. \qquad (3)$$

Here c^0_{IV} is the initial concentration of aliphatic–aromatic amine **IVa**–**IVd**.

The error in k was calculated at a confidence level of 0.95, and the random error in k was no higher than 2–3%. Given are amine no., arenesulfonyl chloride no., and arenesulfonylation rate constant $k \times 10^2$ (l mol^{-1} s^{-1}): **IVa**, **Va**, 0.729 ± 0.005; **IVa**, **Vb**, 0.772 ± 0.009; **IVa**, **Vc**, 3.476 ± 0.073; **IVa**, **Vd**, 3.209 ± 0.038; **IVb**, **Va**, 0.374 ± 0.011; **IVb**, **Vb**, 0.446 ± 0.010; **IVb**, **Vc**, 0.813 ± 0.022; **IVb**, **Vd**, 1.127 ± 0.031; **IVc**, **Vc**, 0.216 ± 0.006; and **IVd**, Vc, 0.156 ± 0.002.

As seen from these data, the effects of substituents in the benzene rings of amines **IVa**–**IVd** and arenesulfonyl chlorides **Va**–**Vd** are opposite to each other: An electron-donor substituent (4-Me) in arenesulfonyl chloride **Vb** decreases reaction rate and the same substituent in amine **Vb** increases it compared with the reaction rate for unsubstituted reagents **IVa** and **Va**.

The effect of substituents in the benzene ring of the arenesulfonylating agent is nicely described by the Hammett equation:

$$\log k = \log k_0 + \rho\sigma. \qquad (4)$$

Here ρ is the sensitivity of the reaction to substituent effect and σ is the Hammett constant of the substituent [8]. With amines **IVa**–**IVd** we used σ^- constants, since they account for conjugation of substituent with reaction center. Equation (4) takes forms (5)–(7) for amines **IVa**, **IVb**, and sulfonyl chloride **Vc**, respectively.

$$\log k = (-2.35 \pm 0.03) + (0.76 \pm 0.07)\sigma; \qquad (5)$$

$$r\ 0.980,\ s\ 0.046,\ n\ 4.$$

$$\log k = (-2.05 \pm 0.04) + (0.76 \pm 0.07)\sigma; \qquad (6)$$

$$r\ 0.990,\ s\ 0.056,\ n\ 4.$$

$$\log k = (-1.87 \pm 0.11) - (1.36 \pm 0.11)\sigma^-, \qquad (7)$$

$$r\ 0.962,\ s\ 0.169,\ n\ 4.$$

Alkyl substituents in the primary amino group of arylamine increase the electron density on the nitrogen atom and accelerate acylation reactions; thus, the rate constant ratio for the reactions of aniline and *N*-methylaniline with benzoyl chloride in benzene is 7.65 [2, 9]. At the same time, as shown in [10], with branched alkyl substituents in the amino group of aromatic amines, steric factor takes significance. Thus, the rate constant ratio for the reactions of aniline and *N*-isobutylaniline with phenacyl bromide is 0.33. In our case, the k value for the reaction of aniline with benzenesulfonyl chloride is ca. 10 times that for the reaction with *N*-isobutylaniline, i.e. the steric factor exerts a stronger kinetic effect than the electronic effect of the alkyl substituent.

The kinetics of arenesulfonylation of amines **IVa**–**IVd** with sulfonyl chloride **Vc** in 2-propanol were studied at 298–318 K. The table lists the rate constants k, errors in their determination, and activation parameters of the reactions studied.

As seen from the table, the arenesulfonylation reaction features low activation energies and changes in the activation entropy. The activation parameters obtained in the present work are nicely consistent with those reported in [2, 11].

Kinetic characteristics of reaction of sulfonyl chloride **Vc** with amines **IVa** and **IVb** in 2-propanol

Amine	T, K	$k \times 10^2$, l mol^{-1} s^{-1}	E_a, kJ/mol	$-\Delta S^{\neq}_{298}$, J mol^{-1} K^{-1}	log B
IVa	298	0.813 ± 0.022	45.5 ± 3.3	139.9 ± 11.0	5.9 ± 0.6
	303	1.040 ± 0.032			
	308	1.279 ± 0.013			
	313	1.893 ± 0.028			
	318	2.276 ± 0.023			
IVb	298	3.476 ± 0.072	30.6 ± 2.8	177.8 ± 9.4	3.9 ± 0.5
	303	3.936 ± 0.063			
	308	4.640 ± 0.073			
	313	5.905 ± 0.035			
	318	6.962 ± 0.053			

EXPERIMENTAL

Chemical grade aniline (**IIa**) was dried over KOH and distilled. Pure grade aldehyde **I** was distilled. Pure grade esters **IIc** and **IId** were used as received. Pure grade sulfonyl chloride **Va** was dried over $CaCl_2$ and distilled in a vacuum. Pure grade sulfonyl chlorides **Vb** and **Vc** were recrystallized from hexane. Sulfonyl chloride **Vd** was synthesized by the procedure in [12] and recrystallized from heptane. Chemical grade 2-propanol was dried over $CuSO_4$ and distilled. Lithium 2,6-dinitrophenolate was obtained from the corresponding phenol and LiOH. Electrolytical hydrogen was used without purification.

Hydrogenative amination of 2-methylpropanal (**I**) with aromatic amines **IVa**–**IVd** was performed in a glass temperature-controlled reactor equipped with a magnetic stirrer (318 K, p_{H_2} 0.1 MPa, solvent 2-propanol, amine : aldehyde ratio 1 : 3; catalyst amount 0.05–0.125 g).

The reactor was charged with 2-propanol, Pd/C, and substrate, after which hydrogen was fed. The process was continued until hydrogen no longer absorbed. The reaction rate was determined volumetrically.

The kinetics of reaction of arylamines with monosubstituted arenesulfonyl chlorides were studied by means of a KFS-2 photoelectrocolorimeter (Poland) equipped with a V7-38 digital voltmeter and a temperature-controlled cell compartment. The working wavelength was 400 nm.

ACKNOWLEDGMENTS

The authors are grateful to the Ministry of Education of the Russian Federation for financial support of the present work in the framework of the *Nauchnye issledovaniya vysshei shkoly v oblasti khimii i khimicheskikh produktov* Scientific and Engineering Program (project no. 003).

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