Regularities of the amino-Claisen rearrangement mechanism

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The synthetic and kinetic regularities of the amino-Claisen rearrangement (ACR) were studied for the transformation of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline. The ACR products are formed due to the conversion of a binary π-complex formed by the reaction of *N*-alkenylaniline hydrochloride with hydrochloride of the solvent (2,5-dimethylaniline).

Key words: Claisen rearrangement, mechanism, 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline.

The amino-Claisen rearrangement (ACR) is an efficient method of *ortho*-alkenylation of arylamines.[1,2] Regioselectivity, simplicity of the technological process, and accessibility of the starting components and catalysts make the ACR to be very attractive in the synthetic respect.

A wide range of unsaturated arylamines became accessible due to practical accomplishment of the ACR. Arylamine derivatives possess a series of useful properties, in particular, pesticidal, antioxidant, and anticorrosion activity. In addition, since the sterically approached NH_2 groups and the *ortho*-alkenyl substituent with the reactive double bond are in the aromatic core of the ACR products, they can be used in the synthesis of many nitrogen-containing heterocyclic compounds (indole, carbazole, quinoline, quinazoline, and benzoxazine derivatives).

Although a considerable number of investigation is devoted to the study of the ACR,[2—4] the mechanism of the amino-Claisen rearrangement has not yet been interpreted unambiguously. Therefore, in this work, we studied the kinetic regularities of the ACR of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline in a medium of 2,5-dimethylaniline.

Experimental

The components of the reaction system were identified using modern physicochemical methods of analysis. GLC analysis was carried out on a Chrom-5 chromatograph with a flame-ionization detector (column 1200×3 mm with 5% SE-30 on Chromatone N-AW-HMDS) using helium as a carrier gas. The physicochemical and spectral characteristics of compounds **1a**,**b** correspond to those published earlier.[1] Aniline (GOST 313-77), *N*,*N*-dimethylaniline (GOST 5855-78), and nitrobenzene (GOST 6350-56) were purified by standard procedures.[5]

The kinetics of the amino-Claisen rearrangement was studied as follows. A mixture of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline (**1a**) hydrochloride or 3,6-dimethyl-2-(pent-3-en-2-yl)aniline hydrochloride (**2a**) (22.6 g, 0.1 mol) and 100 mL of the corresponding solvent, *viz.*, 2,5-dimethylaniline, aniline, or nitrobenzene, was heated for 1—3 h at 150—190 °C. The composition and concentration of the products were determined by GLC. The compounds in the mixture were identified by comparing the retention times of the obtained samples and the corresponding pre-synthesized individual substances.

Results and Discussion

Two possible mechanisms of the catalytic ACR, namely, intra- and intermolecular, are presently assumed in the literature.[1,2] The intramolecular mechanism is a one-stage concerted [3,3]-sigmatropic rearrangement of the protonated form of arylamines with the pericyclic transition state.[3,4] The intermolecular mechanism includes the elimination of the allyl carbocation (with the formation of either a π-complex in the solvent cage, or a solvate-separated ion-molecular pair) and its electrophilic attack

† Deceased.

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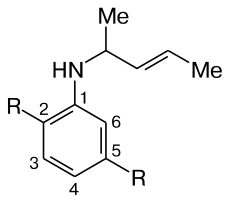
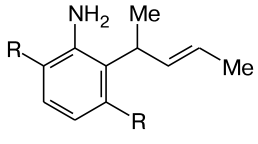
to the *ortho*- or *para*-position of the aromatic core of arylamine.

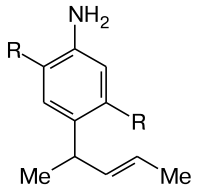
One of the most interesting objects for studying the amino-Claisen rearrangement is 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline (**1a**), whose uniqueness is an unusual easiness of formation of both *ortho*- (**2a**) and *para*-isomers (**3a**).



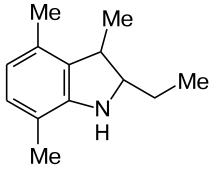
1a,b



2a,b



3a,b



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1—3: R = Me (**a**), H (**b**)

The catalytic amino rearrangement of compound **1a** occurs in the presence of HCl in a 2,5-dimethylaniline solution at 150—200 °C for 1—4 h. An analysis of the reaction mixture revealed that the composition of the intermediate and final ACR products depends on the nature of the solvent used.

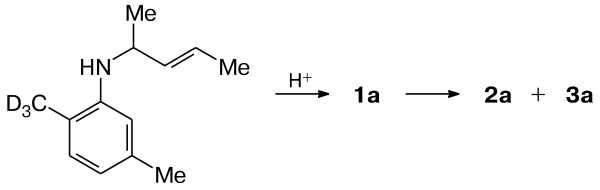
3,6-Dimethyl-2-(pent-3-en-2-yl)aniline (**2a**), 2,5-dimethyl-4-(pent-3-en-2-yl)aniline (**3a**), and 2-ethyl-3,4,7-trimethylindoline (**4**) are formed due to the rearrangement in 2,5-dimethylaniline. In this conversion, *ortho*-isomer **2a** acts as an intermediate product, while *para*-isomer **3a** (70%) and dihydroindole **4** (3—5%) are the final products. This was proved by the transformation of compound **2a** (isolated from the reaction mixture) into products **3a** and **4** in the presence of HCl in 2,5-dimethylaniline at 170 °C.

The rearrangement of hydrochloride **1a** in an aniline medium also affords rearrangement products **2a** and **3a**. However, up to 20% of products of the transfer of the alkenyl group from molecule **1a** to the aniline molecule to form *N*-(pent-3-en-2-yl)aniline (**1b**) and 2-(pent-3-en-2-yl)aniline (**2b**) were simultaneously observed in the reaction mixture. The presence of 2,5-dimethylaniline in the reaction mixture indicates that hydrochloride **1a** lost the alkenyl cation.

In nitrobenzene the rearrangement of **1a** proceeds *via* the intermediate formation of **2a** and also completes by the formation of **3a** and **4**. In the absence of a catalyst, *ortho*-isomer **2a** isolated from the reaction mixture forms *para*-isomer **3a** neither in heptadecane nor in nitrobenzene even at 250 °C, but gives the cyclization product 2-ethyl-3,4,7-trimethylindoline (**4**).

These results unambiguously indicate that the ACR is a complicated multistage process in which the solvent plays a substantial role. This conclusion is brightly confirmed by the results of an experiment with 2-deuteromethyl-5-methyl-*N*-(pent-3-en-2-yl)aniline (**5**). The study of the ACR of labeled *N*-alkenylarylamine in 2,5-dimethylaniline showed that already at 30% conversion the starting substrate **5** is transformed into compound **1a** by 50% and further into *ortho*- and *para*-isomers **2a** and **3a** containing no isotope labels (Scheme 1).

Scheme 1



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For 80% conversion, the transformation products of **5** are compounds **1a**, **2a**, and **3a** containing no deuterium atoms.

Since the solvent exerts different effects on the occurrence of the ACR, the kinetic regularities of the isomerization of compound **1a** were studied in a medium of 2,5-dimethylaniline.

Kinetic regularities of the ACR of compound 1a in a medium of 2,5-dimethylaniline. The typical kinetic curves of the ACR of hydrochloride **1a** are shown in Fig. 1.

Figure 1 shows that the *ortho*- and *para*-isomers are the major rearrangement products and at the initial reaction moment (before 10 min) they are accumulated with

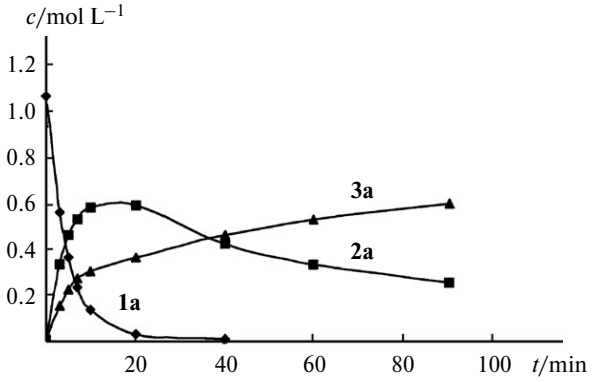


Fig. 1. Kinetic curves for the consumption of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline (**1a**) and accumulation of 3,6-dimethyl-2-(pent-3-en-2-yl)aniline (**2a**) and 2,5-dimethyl-4-(pent-3-en-2-yl)aniline (**3a**). Reaction conditions: 170 °C, $[\mathbf{1a}]_0 = [HCl]_0 = 1.07$ mol L^{-1}, 2,5-dimethylaniline.

Scheme 2

$$Me_2C_6H_3NHC_5H_9\ (\mathbf{1a}) + H^+ \overset{K_1}{\rightleftharpoons} Me_2C_6H_3{-}N^+H_2C_5H_9 \quad (1)$$

$$Me_2C_6H_3{-}NH_2 + H^+ \overset{k_2}{\rightleftharpoons} Me_2C_6H_3{-}N^+H_3 \quad (2)$$

$$Me_2C_6H_3{-}NH_2^+C_5H_9 + Me_2C_6H_3{-}N^+H_3 \overset{k_3}{\rightleftharpoons} Me_2C_6H_3{-}N^+H_2C_5H_9 \rightleftharpoons H_3N^+{-}C_6H_3Me_2\ (\mathbf{A}) \quad (3)$$

$$\mathbf{A} \xrightarrow{k_4} Me_2C_6H_3{-}NHC_5H_9 + H^+ + Me_2C_6H_3{-}NH_3^+ \quad (4)$$

$$\mathbf{A} \xrightarrow{k_5} Me_2(2\text{-}C_5H_9)C_6H_2{-}NH_3^+ + Me_2C_6H_3{-}NH_3^+ \quad (5)$$

$$\mathbf{A} \xrightarrow{k_6} Me_2(4\text{-}C_5H_9)C_6H_2{-}NH_3^+ + Me_2C_6H_3{-}N^+H_3 \quad (6)$$

$$\mathbf{A} \xrightarrow{k_7} C_5H_8 + Me_2C_6H_3{-}NH_3^+ + Me_2C_6H_3{-}N^+H_3 \quad (7)$$

$$Me_2(2\text{-}C_5H_9)C_6H_2{-}NH_3^+ + Me_2C_6H_3{-}NH_3^+ \overset{k_8}{\rightleftharpoons} Me_2(2\text{-}C_5H_9)C_6H_2{-}N^+H_3 \rightleftharpoons H_3N^+{-}C_6H_3Me_2\ (\mathbf{B}) \quad (8)$$

$$\mathbf{B} \xrightarrow{k_9} Me_2(4\text{-}C_5H_9)C_6H_2{-}NH_3^+ + Me_2C_6H_3{-}NH_3^+ \quad (9)$$

$$\mathbf{B} \longrightarrow (\mathbf{4})H^+ + Me_2C_6H_3{-}NH_3^+ \quad (10)$$

the constant molar ratio **2a** : **3a** = 1.95±0.05. This prejudices the scheme of consecutive formation of **3a** from **2a** at the initial reaction stage. Most likely, the *ortho*- and *para*-isomers are accumulated in parallel in the initial period of the reaction. However, after *N*-isomer **1a** was consumed, *para*-isomer **3a** continues to form with a simultaneous decrease in the concentration of *ortho*-product **2a**. Therefore, **2a** is gradually transformed into **3a** at a deep conversion of the initial reagent **1a**. As can be seen from Fig. 1, the concentration of *para*-isomer **3a** increases more slowly than the concentration of *ortho*-isomer **2a** decreases because of the partial occurrence of cyclization of **2a** with the formation of **4**. Under all experimental conditions studied (variation of the temperature and concentration of **1a** and the catalyst), the kinetic curves of consumption of *N*-isomer **1a** are linear in the coordinates of the first-order reaction equation, *i.e.*, $V_0 = k_{eff} \cdot [\mathbf{1a}]$ (Fig. 2).

According to the accepted literature concepts, it should be expected that the reaction order of consumption of **1a** with respect to the catalyst is also equal to unity. However, it turned out that the reaction orders with respect to the catalyst for the consumption of **1a** and accumulation of **2a** and **3a** are equal to two (Fig. 3).

The second order with respect to HCl suggests that an intermediate formed from protonated **1a** and a protonated solvent molecule (2,5-dimethylaniline) appears in the reaction under study. Taking this into account, the regularities of the amino-Claisen rearrangement of compound **1a** in a solution of 2,5-dimethylaniline can be described by Scheme 2.

In presented Scheme 2, the key intermediate is binary π-complex **A**, whose formation is equilibrium from the protonated forms of the starting substrate and solvent (reaction (3)). The interaction of the protonated amino group of compound **1a** with π-electrons of the aromatic ring of the protonated solvent partially disturbs the benzene ring aromaticity, due to which the migration of the alkenyl C_5H_9 group is facilitated with the formation of the *ortho*- and *para*-isomers. Taking into account steric hin-

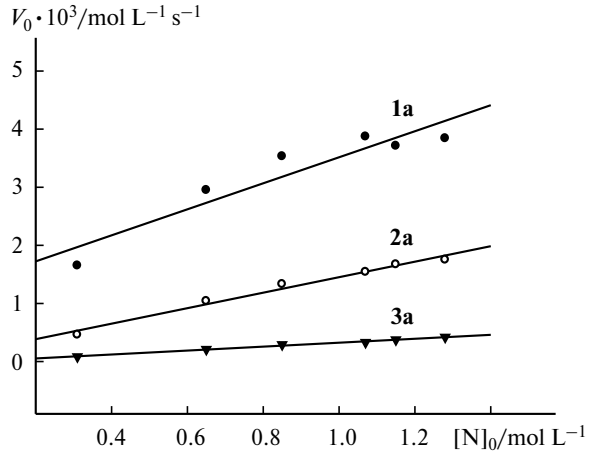


Fig. 2. Initial rates of consumption of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline (**1a**) and accumulation of 3,6-dimethyl-2-(pent-3-en-2-yl)aniline (**2a**) and 2,5-dimethyl-4-(pent-3-en-2-yl)-aniline (**3a**) *vs* initial concentration of compound **1a** ([N]$_0$) in the presence of HCl ([HCl] = 1.07 mol L^{-1}).

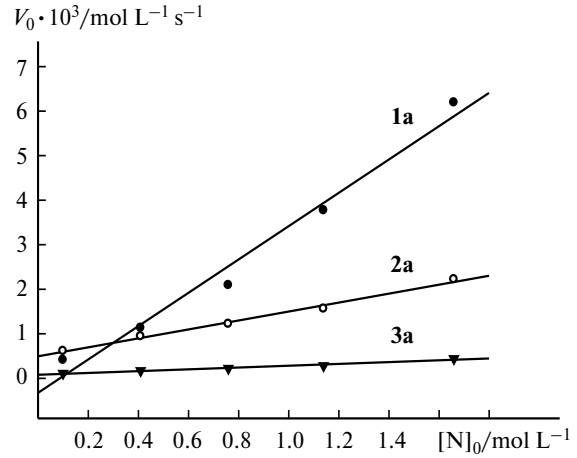


Fig. 3. Initial rates of consumption of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline (**1a**) and accumulation of 3,6-dimethyl-2-(pent-3-en-2-yl)aniline (**2a**) and 2,5-dimethyl-4-(pent-3-en-2-yl)-aniline (**3a**) *vs* initial concentration of HCl ([**1a**] = 1.07 mol L^{-1}).

drances, it can be assumed that the *ortho*-isomer is formed *via* the intramolecular mechanism through transition state **A** due to C_5H_9 group migration to the *ortho*-position of its own molecule *via* reaction (5). At stage (8) the protonated form of the *ortho*-isomer undergoes isomerization in the reaction with the protonated form of the solvent to form the binary π-complex, *i.e.*, intermediate **B**. It is most probable that the *para*-isomer is formed upon the migration of the C_5H_9 substituent to the *para*-position of the benzene ring of the solvent *via* reaction (6) (intermolecular mechanism). This isomer can also be formed intramolecularly from the *ortho*-isomer *via* reaction (9) through transition state **B**. The inversion of the alkenyl group should be observed in reactions (5) and (9). In fact, it was established in a model experiment (Scheme 3) that compounds **7**—**9** are the rearrangement products of 2,5-dimethyl-*N*-(5-methylhex-3-en-2-yl)aniline (**6**).

The formation of the single *ortho*-isomer with inverted alkenyl radical **7** indicates the intramolecular mechanism of the rearrangement. On the contrary, the formation of two *para*-isomers **8** and **9** (with and without inversion of the allyl radical) indicates two routes: product **8** is formed, most likely, *via* reaction (6) by C_5H_9 group migration (see Scheme 2) to the solvent molecule following the intramolecular mechanism, whereas compound **9** is probably formed *via* reaction (9) (see Scheme 2) through the transition state binding the *ortho*- and *para*-carbon atoms of the starting substrate (intramolecularly). The route of *para*-isomer formation through stages (5) and (9) includes, in fact, the double inversion of the alkenyl radical. Stages (7) and (10) describe possible side reactions during the ACR. Stage (4) explains the composition of the transalkylation products of the deuterated *N*-isomer in a 2,5-dimethylaniline medium (see Scheme 2).

According to Scheme 2, it can be assumed that the rate-determining steps of the ACR are the stages of transformation of complex **A**, *i.e.*, stages (4)—(7). Therefore, the rate of consumption of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline (**1a**) (V_N) will be represent the algebraic sum of rates of stages (4), (5), (6), and (7)

$$V_N = V_5 + V_6 + V_7 - V_4 = (k_5 + k_6 + k_7 - k_4)[A] = \\ = (k_5 + k_6 + k_7)[A] - k_4[A]. \quad (11)$$

In Eq. (11) rate V_4 was taken with minus, because at stage (4) the starting *N*-isomer is not consumed but is formed. The concentration of complex **A** can be found from the equilibrium condition of stage (3)

$$[A] = K_3[Me_2C_6H_3NH_2^+ - C_5H_9][Me_2C_6H_3 - NH_3^+]. \quad (12)$$

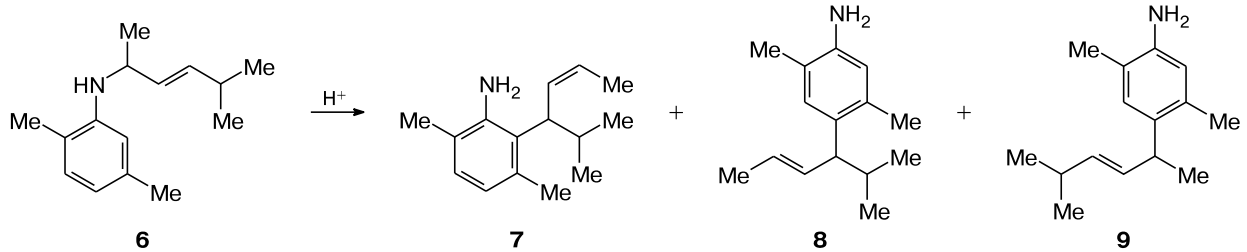
In turn, the concentrations of protonated forms of the starting substrate and solvent are related by equilibria (1) and (2) with the initial concentrations of the reactant, solvent, and catalyst

$$[Me_2C_6H_3 - NH_2^+ - C_5H_9] = \\ = K_1[Me_2C_6H_3 - NHC_5H_9][H^+], \quad (13)$$

$$[Me_2C_6H_3 - N^+H_3] = \\ = K_2[Me_2C_6H_3 - NH_2][H^+]. \quad (14)$$

Equations (12) and (14) were obtained under the assumption that the equilibrium of stages (1)—(3) is not violated due to the consumption of the final products of these stages in subsequent reactions. Taking into

Scheme 3



6 **7** **8** **9**

account Eqs (12)—(14), Eq. (11) is transformed into the form

$$V_N = (k_5 + k_6 + k_7)K_1K_2K_3[Me_2C_6H_3—NHC_5H_9]\cdot$$
$$\cdot[Me_2C_6H_3—NH_2]\,[H^+]^2 - k_4K_1K_2K_3,$$

where

$$[Me_2C_6H_3NH—C_5H_9][Me_2C_6H_3—NH_2][H^+]^2 =$$
$$= const_1[Me_2C_6H_3NH—C_5H_9][Me_2C_6H_3—NH_2][H^+]^2 -$$
$$- const_2[Me_2C_6H_3—NHC_5H_9][Me_2C_6H_3—NH_2][H^+]^2. \quad (15)$$

The rates of accumulation of the *ortho*- (V_{ortho}) and *para*-isomers (V_{para}) with allowance for Eqs (12)—(14) can be presented as follows:

$$V_{ortho} = v_5 = k_5[A] = k_5K_1K_2K_3[Me_2C_6H_3—NHC_5H_9]\cdot$$
$$\cdot[Me_2C_6H_3—NH_2][H^+]^2, \quad (16)$$

$$V_{para} = v_6 = k_6[A] = k_6k_1k_2k_3[Me_2C_6H_3—NHC_5H_9]\cdot$$
$$\cdot[Me_2C_6H_3—NH_2][H^+]^2. \quad (17)$$

According to Eqs (15)—(17), the reaction order with respect to the catalyst is two and the partial reaction orders with respect to the starting substrate and solvent are unity. The reaction rates depend on the rate constants of the elementary steps in which the reactant is consumed and the reaction products are formed and also depend on the equilibrium constants of stages (1)—(3).

Equations (15)—(17) predict that the consumption rates of the starting *N*-isomer and the accumulation rates of the *ortho*- and *para*-isomers at constant initial concentrations of the starting substrate and solvent should increase non-linearly with an increase in the catalyst concentration, which is experimentally observed (see Fig. 3).

The revealed kinetic regularities of the amino-Claisen rearrangement are retained in the whole temperature range studied from 150 to 190 °C.

The initial rates of consumption of the *N*-isomer and accumulation of the *ortho*- and *para*-isomers depend linearly on the temperature in the Arrhenius coordinates from where the activation energies (E^*) of the considered stages were estimated.

Stage	E^*/kJ mol^{-1}
Consumption of **1a**	116
Consumption of **2a**	114
Consumption of **3a** (initial stage)	80

The *para*-isomer is formed with a lower activation energy compared to that of the *ortho*-isomer. It is most likely that the intermolecular migration of the C_5H_9 allyl substituent to the *para*-position of the solvent molecule at stage (6) requires lower energy expenses compared to the intramolecular route of *ortho*-isomer formation at stage (5).

Thus, the complex study of the synthetic and kinetic aspects of the acid-catalyzed isomerization of 2,5-dimethyl-*N*-(pent-3-en-2-yl)aniline provides new concepts on the mechanism of the amino-Claisen rearrangement, which includes the equilibrium stage of formation of the binary π-complex from hydrochlorides of the starting amine and solvent with its subsequent transformation into the *ortho*- and *para*-isomers.

References

1. I. B. Abdrakhmanov, Doct. (Chem.) Thesis, Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, 1989, 323 pp. (in Russian).
2. R. P. Lutz, *Chem. Rev.*, 1984, **84**, 205.
3. X. Peng, M. Dongfeng, Zh. Yunqing, *Youji Hauxae* [*Chin. J. Org. Chem.*], 1986, **6**, 226.
4. *The Claisen Rearrangement: Methods and Applications*, Eds M. Hiersemann, U. Nubbemeyer, Wiley-VCH Verlag, Weinheim, 2007, 591 pp.
5. L. F. Tietze, Th. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, Georg Thieme Verlag, Stuttgart, 1991, 649 S.

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