Nucleophilic substitution reaction of the acyl azides with secondary amines mediated by Copper(II) salt

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We have studied the Copper (II) Salt-Mediated Reaction of nucleophilic substitution of the azide group of acyl azide by secondary amine group. In the course of the reaction copper (II) azide, acetic acid and the corresponding amide are formed. On the basis of IR spectra of reaction products we have concluded that there is the absorption band shifts of the stretching vibrations of azide group, which explains the formation of an intermediate complex with copper (II) acetate. Characteristic to the Copper (II) acetate blue-green color of the solution changes to brown color of the Copper (II) azide solution. It can be used as a characteristic "color" or a quantitative test, to determine amount of acyl azide and the secondary aliphatic amines.

Key words: acyl azide, Copper(II) acetate, Copper(II) azide, Nucleophilic azide group substitution, Piperidine, Copper(II) complex, amine acylation, azide organic acid.

Previously, in the study of the acyl azide-copper acetate(II) coordination and in the presence of secondary aliphatic amines traces in acetonitrile we observed an instant change in color of the reaction mixture from blue-green to brown. Replacing the solvent to THF, DMF, and acetone did not influence upon the course of the reaction. Since the analysis of the literature did not revealed any description of the phenomenon the reaction has been studied in detail. The study was the ultimate goal of this work.

Our objects were: benzoyl azide **1a** and diazide of terephthalic acid **1b**. We used acetate of copper (II) as a copper (II) salt; and piperidine as an amine. Reaction was performed in DMF, acetonitrile and mixture of acetone : water (1:9, v/v).

Experimental part

IR spectra of the obtained compounds were measured by means of IR-spectrophotometer Analytik Jena SPECORD 75-IR in nujol mull and in crushed drops between KBr and NaCl plates. NMR spectra ^{13}C measured by means of Bruker AM-300 spectrometer in $CDCl_3$, internal standard - $SiMe_4$. UV/Vis-spectra of absorption were measured by Analytik Jena SPECORD 40 spectrophotometer. Preparative column chromatography with silica gel LS 5/40 and alumina L 5/40 and chloroform (chemical pure type) as an eluent was used for preparative isolation of the reaction products. Thin layer chromatography (TLC) was realized on plates Sorbfil (silica gel CTX-1A), mixture of toluene with methanol (5:2, v/v).

General method of acyl azides synthesis. In thick wall glass with volume of 500 ml 0.1 mole of dry acid hydrazide was dissolved in 200 ml of 1.0 N HCl. The solution of 8 g (excess) of $NaNO_2$ in 50 ml of water was added to cooled down to 0-5 ^{0}C solution under intensive stirring. Azide was precipitated in the form of loose, colorless crystals. The crystals were separated and reprecipitated from acetone with water, and then dried in vacuum under cooling. Due to low thermal stability the azide obtained was stored at –18 °C. IR-spectra, ν/cm^{-1}: **1a** - 2160, 2120 (ν_{as} N_3); 1260 (ν_s N_3); 1680 (C=O); **1b** – 2160, 2115 (ν_{as} N_3); 1260 (ν_s N_3); 1665 (C=O).

Results and discussion

Anion of copper (II) acetate absorbs in short-wavelenghth part of UV-spectra and does not interfere an investigation of influence of complex formation by acyl azide due to shifts of their bands in the electronic spectra.

Addition of copper (II) acetate (in molar ratio 1:1) into solution of **1a** the band of the azide absorption at 260 nm was shift to the short wavelength region by 10 nm. We explain the shift by building of the azide into coordination sphere of the copper ion and by complex formation. Hypsochromic shift of the π-π* absorption band of **1a** in the case of coordination says about an increase of the energy gap between S_0 and S_1 electronic states of the azide that is a reason of an increase of bond order on the π-system of chromofor. However, we cannot say certainly what fragment (azide group or carbonyl bond) is changed upon the complex formation. Due to partial joining of their π-system it is possible to say about interaction of copper (II) acetate with both groups simultaneously, that is the copper(II) acetate coordinates onto acyl azide group as whole.

In analogy, comparison of UV-spectra of solutions of **1b** in acetonitrile and of mixture of **1b** with copper (II) acetate there is observed a shift of the absorption maximum of the azide absorption to the long wavelength region from 255 to 265 nm. The latter also says about coordination of **1b** by ion copper (II).

Multidirectional hypsochromic for **1a** and bathochromic to **1b** the absorption maxima shifts at the complex seems to be initiated by the possibility of forming of a conjugate structure of **1b**, with the simultaneous coordination of both groups atsilazidnyh **1b** salt of copper.

When comparing the electronic absorption spectra of solutions of copper acetate (II) and its mixture with acyl azide in acetonitrile it was not registered a shift intrametallic d-d* transition of copper acetate (II), (λ_{max} = 700 nm)[1].

As both in acetonitrile, and in DMF an addition to the complex of **1b** with copper acetate (II) piperidine leads to changing of the solution original color from blue-green to brown. In the electronic absorption spectrum of this solution there appeared absorption band with a maximum at 395-420 nm, which is absent in the spectra of the initial mixture. The reaction takes place completely within 8 min.

When used as a solvent mixture of acetone: water in a volume ratio of 1: 9 out of the reaction products has not changed.

Adding of piperidine to a solution of **1a** with copper acetate (II) also resulted in the formation of a similar product of the reaction, the absorption maximum which coincides with the absorption maximum of the product formed in the reaction with **1b**.

Brown grained precipitate was separated bydeposition from solutions in acetonitrile with chloroform. When comparing the IR spectra of the isolated product in the reaction of 1b with the IR spectrum of the azide itself there was detected shift of the absorption bands of asymmetric and symmetric stretching vibrations of the azide group in the long-wavelength range by 75 and 35 cm^{-1}, respectively, from 2115 and 1260 to 2040 and 1225 cm^{-1} . Asymmetric stretching vibration of the carbonyl group was shifted to longer wavelengths by 35 cm^{-1}, from 1665 to 1630 cm^{-1} (Fig. 1).

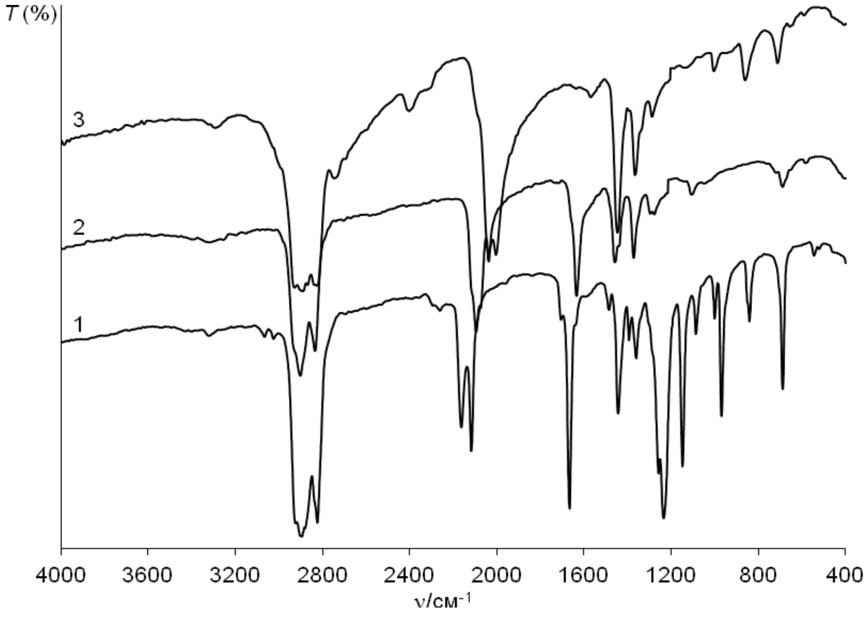


Fig.1. IR-spectra of nujol mull of ***1b*** *(1), complex of* ***1b*** *with piperidine and with copper acetate (2), and copper (II) azide (3).*

According to the literature[2] the shift to longer wavelengths of the absorption band of the asymmetric stretching vibration of the azide group indicates a decrease in the degree of bondage of the azide and carbonyl groups.

After dissolution of the product in acetonitrile with addition of small amount of chloroform used as a precipitant, shiny, dark-brown, needle-like crystals were slowly formed. Their IR spectra differ from the IR spectra of the precipitate (Fig. 2). The absorption band of the asymmetric stretching vibration of the azide group in the spectrum of needle crystals shifted to the red by 40 cm^{-1} (from 2040 to 2000 cm^{-1}) relative to the original product. The absorption bands of the stretching vibration of the carbonyl group and the symmetric stretching vibration of the azide group disappeared. Further shift of asymmetric and symmetric stretching vibrations of the disappearance of the azide group in the IR spectrum of the needles says about ionization[2] of azide. In the case the appearance of the absorption bands of the asymmetric stretching vibration of the isocyanate group was not found.

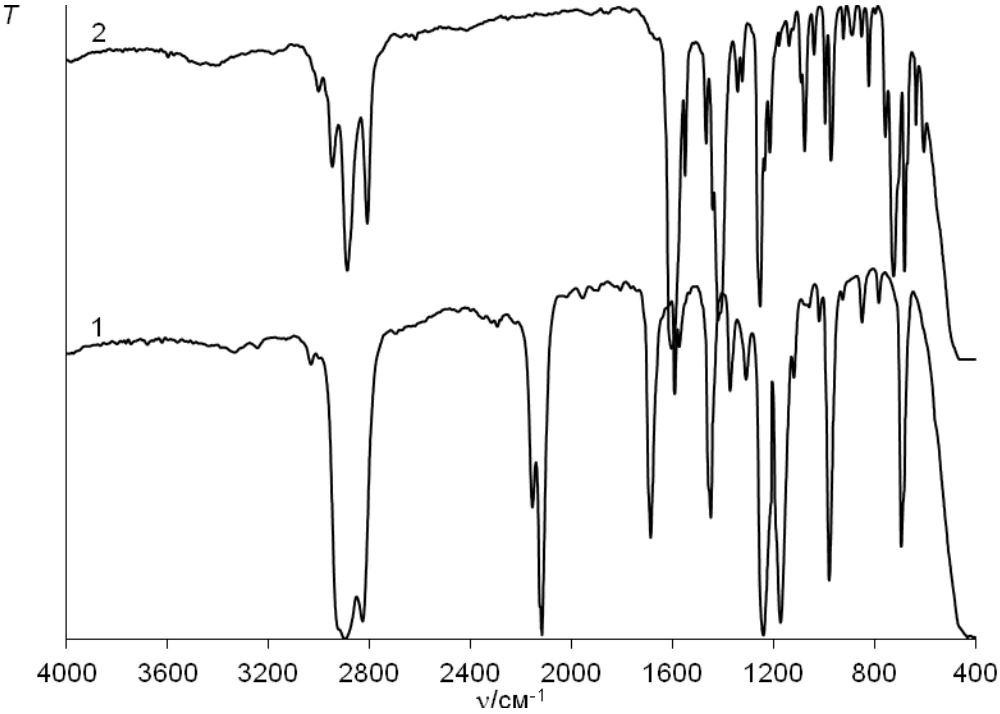


*Fig.2. IR spectra of nujol mull of **1a** (1) and of **2a** in liquid film (2).*

Thus, in the course of the reaction there is a gradual decrease in the bond order of between azide and carbonyl groups. As a result the decomposition ends by breaking of bond with the formation of azide of copper (II) and acetic acid (Scheme, reaction (b)). The formation of acetic acid was found by a characteristic odor. CAUTION: The crystals are formed after drying explodes in friction.

Study of the colored products of the reaction of the azides with piperidine in the presence of copper acetate (II), and in particular the evolvement of azide copper (II), suggest that the process is a nucleophilic substitution reaction. In the reaction, the azide group will be the leaving group and, therefore, the reaction products are the corresponding amides.

After preparative separation of the products of interaction of **1b** with copper acetate and piperidine by column chromatography there were separated two white crystalline substance.

IR spectrum of substance I (Fig. 3) has an absorption band with a maximum at 2140 cm^{-1}, that is interpreted as asymmetric stretching vibration of the azide group. Absorption band at 1680 cm^{-1} was assigned to the stretching vibration of the carbonyl group and the band at 1615 cm^{-1} was assigned to the stretching vibration of the C = C bond of benzene ring. For comparison, it is desirable to note that the IR spectrum absorption band of azide group in 1b is located at 2160, 2115 cm^{-1}, and the carbonyl group at 1665 cm^{-1}. Consequently, the substance I contains the aryl azide group.

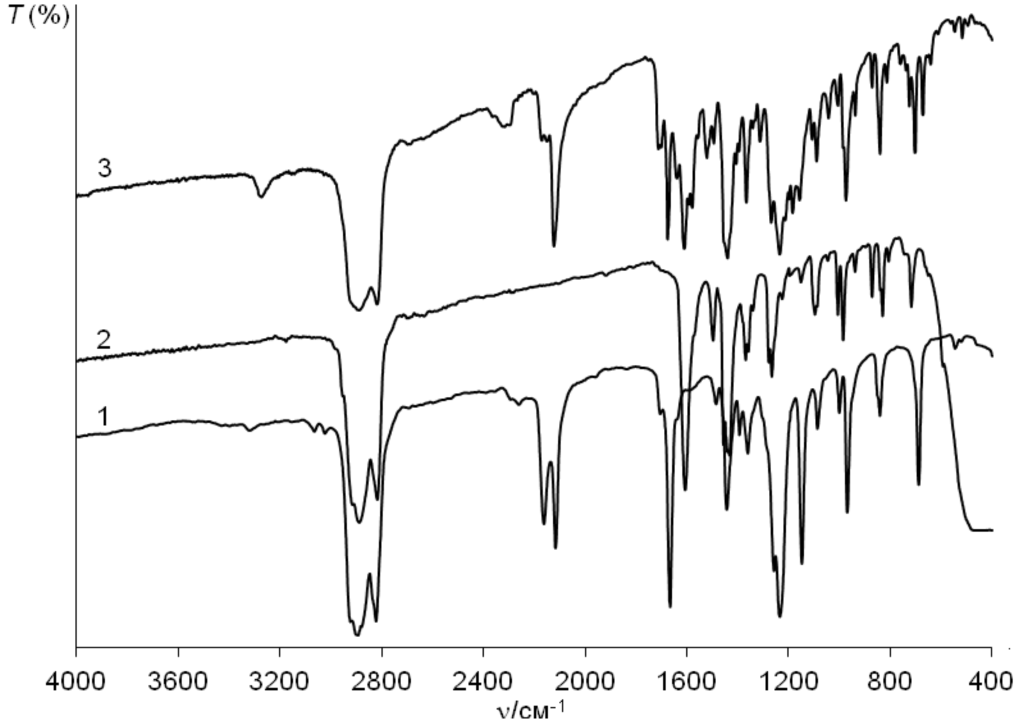


*Fig.3. IR spectra of nujol mull of **1b** (1), **2b** (2), azidopiperidylamide of terephthalic acid (3).*

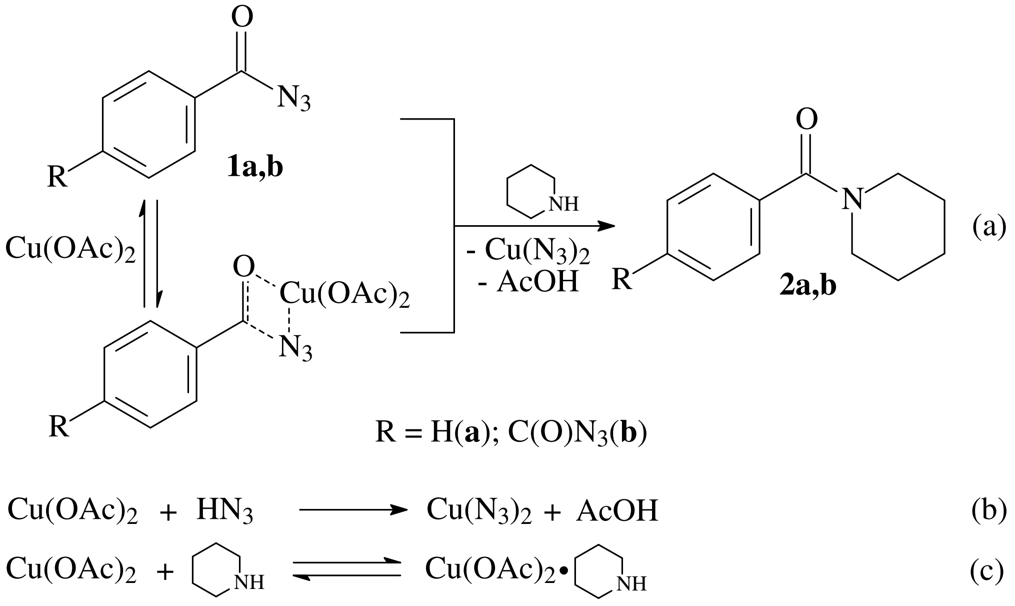
The IR spectrum of substance II contains the absorption band at 1615 cm^{-1} and no absorption bands of stretching vibrations of the azide and carbonyl (1680 cm^{-1}) groups (Fig. 3).

The ^{13}C NMR ($CDCl_3$) spectrum of II allowed to interpret this product as dipiperidilamid terephthalic acid **2b**. Consequently, the matter is **I** azidopiperidilamid terephthalic acid due to the characteristic absorption δ_C at 169.523 ppm (C=O). Consequently, **I** is azidopiperidilamid of terephthalic acid.

Chromatography study of the reaction products from reaction of **1a** with copper acetate and piperidine reveals formation of a substance that is a liquid of a pale yellow color. In IR spectrum of it there the absorption band at 1640 cm^{-1} that is attributed to the stretching vibration of carbonyl group. The absorption band of the asymmetric stretching vibration of the azide group **1a** is absent. From comparison of the IR spectrum of this compound and of **2b** the isolated product was identified as piperidilamid of benzoic acid (1-benzoyl piperidine) **2a**.

Thus, the formation of amides of aromatic acids confirmed the assumption of the reaction of nucleophilic substitution, in which the leaving group is the azide one. Also it was found that one of the products of the reaction is HN_3. Copper acetate interact with it to form the azide copper (II), thus shifting the equilibrium reaction towards the nucleophilic amide.

The formation of complexes with amines is characteristic for salts of copper (II)[3]. Therefore, in the case of the interaction of acyl azide with copper acetate and piperidine there two processes are in competion. They are nucleophilic substitution (Scheme, the reaction of (a)) and the complexation of copper acetate and piperidine (Scheme, reaction (b)). Obviously, the second reaction leads to a decrease of the concentration of piperidine in the solution, that can affect the depth of the reaction of nucleophilic substitution.



Scheme. Probable mechanism of nucleophilic substitution reaction between acyl azides and secondary amines mediated by Copper(II) salt.

With 4-fold molar excess of copper acetate (II) in a solution nucleophilic substitution proceeds with the greatest speed. Increase in excess of copper salt leads to inhibition of the reaction that caused the decrease of concentration of piperidine in solution due to the shift of the equilibrium towards the formation of its complex with copper acetate (II). As the concentration of copper salts in the solution increases formation of piperidine-copper complex begins to dominate over the nucleophilic substitution, and its rate being increasing in the beginning began to be declining afterwards. However, since the coordination of amine and copper acetate is reversible the presence of the corresponding complex in the reaction mixture maintained some constant concentration of piperidine in the reaction. Thus, the consumption of copper salts and piperidine in the nucleophilic substitution and dissociation of the piperidino-copper complex of increases concentration of piperidine.

The observed change of color in the course of the reaction of acyl azides with secondary amines in the presence of salts of copper (II) can be used as high-quality, "color" reaction suitable to find both acyl azide and secondary aliphatic amines and in the case of more scrupulous study it is a quantitative one. The appearance of the characteristic brown color of the solution was observed not only for the investigated aromatic azides, but for the aliphatic acid azides. The diazide of stearic and succinic acid were used to check the assumpton. Diethylamine was also used as a secondary amine.

Thus, this reaction is characteristic for azides, derived both aromatic and aliphatic acids, that is, it seems to be a characteristic reaction for all types of acyl azides.

Reference

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