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5-Acylmethyl-3-(2-pyridyl)-1,2,4-triazines: Synthesis and Complexes with Cu(II)

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Abstract—5-Acylmethyl-3-(2-pyridyl)-1,2,4-triazines are easily prepared from accessible 3-(2-pyridyl)-1,2,4-triazine 4-oxides by reaction of the latter with acetophenone or trifluoroacetone in the presence of NaH. The compounds obtained behaved as efficient ligands in reaction with $CuCl_2$ furnishing dimeric neutral complexes with Cu(II) whose structure was investigated by means of X-ray diffraction analysis.

A considerable interest to heterocyclic substances containing both pyridine and 1,2,4-triazine rings is due to their pronounced ability to form coordination compounds with transition metals. For instance, derivatives of pyridyl-1,2,4-triazine are used as sensitive analytical reagents for iron ions [1, 2]. 2,6-Bis(5,6-dialkyl-1,2,4-triazin-3-yl)-pyridines are selective extractants applied to partitioning of actinides and lanthanides in the course of recovery of the used nuclear fuel [3, 4]. An opportunity was also demonstrated [5, 6] of transforming pyridyl-1,2,4-triazines into functionalized polypyridines (bi- and terpyridines), ligands extensively used in the coordination, analytical, and supramolecular chemistry [7, 8].

Up till now the most widely used preparation method for pyridyl-1,2,4-triazines consisted in the cyclization of pyridylamidrazones with diketones [9]. The disadvantage of this method lies in a limited possibility to vary substituents and consequently in restricted optimization of the useful properties. We recently developed a sufficiently simple procedure for the synthesis of 3-pyridyl-1,2,4-triazine ligands involving the preparation of 3-(2-pyridyl)-1,2,4-triazine 4-oxides and the functionalization of the heterocyclic ensemble via a nucleophilic substitution of a hydrogen in the 1,2,4-triazine ring [10]. The presence of the N-oxide group significantly facilitates these reactions [11].

The target of this study was the development of synthetic methods for new heterocyclic N,N,O-ligands, 5-acylmethyl-3-(2-pyridyl)-1,2,4-triazines **I** that alongside the bidentate heterocyclic ensemble possessed a chelating carbonyl group in the side chain.

We selected as the starting compounds the substances we had described before [10], 6-aryl-3-(2-pyridyl)-1,2,4-triazine 4-oxides **II–IV**.

It was established that compounds **II–IV** readily reacted with carbanions generated from acetophenones or from trifluoroacetone. The reaction occurred [12] as the carbanion addition to the C^5 atom of the triazine ring followed by *auto*-aromatization of the intermediate σ^H-adducts through water elimination to furnish in 50–85% yields the products of aromatic substitution: 5-phenacyl- or 5-trifluoroacetylmethyl-3-(2-pyridyl)-1,2,4-triazines **Ia–Ig** (see the scheme).

As an independent synthesis of these compounds we performed the previously described cyano group substitution in a series of 5-cyano-1,2,4-triazines [13]. For instance, the reaction of acetophenone carbanion with 3-(2-pyridyl)-6-phenyl-5-cyano-1,2,4-triazine (**V**) obtained by direct cyanation [14] of 1,2,4-triazine 4-oxide (**II**) resulted in compound **Ia** (see the scheme). This reaction may be regarded as an alternative method of synthesis for ligands **I**, although it is less preferable primarily not because of the additional cyanation stage but due to lower yields caused by the tarring of the reaction mixture.

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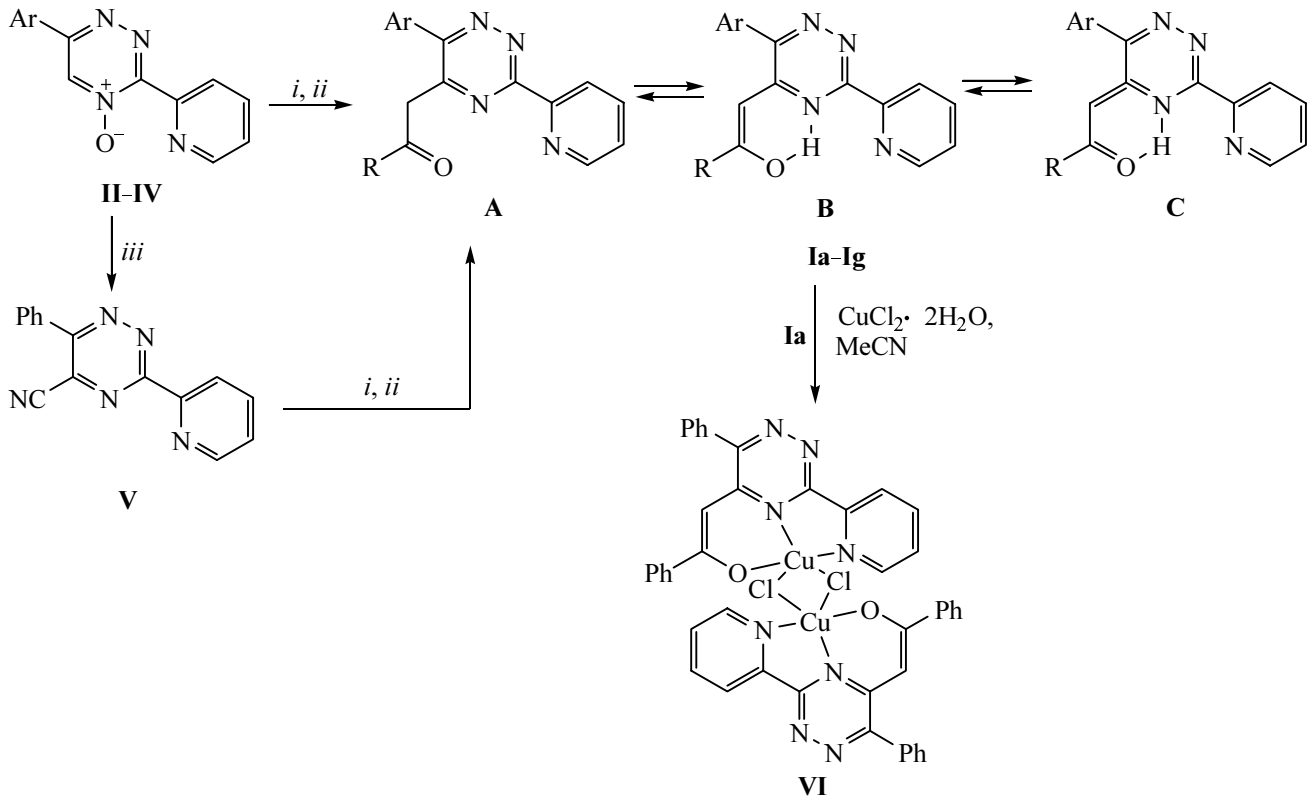


I, R = Ph (**a**), 4-ClC_6H_4 (**b**), tolyl (**c**), 4-FC_6H_4 (**d**), CF_3 (**e–g**); Ar = Ph (**Ia–Ie, II**), 4-ClC_6H_4 (**If, III**), 4-$MeOC_6H_4$ (**Ig, IV**). Reagents and conditions: *i*, $RCOCH_3$, NaH, THF, –20°C, 20 min, then triazine *ii*, –20°C, 3 h; *ii*, HOAc; *iii*, acetone cyanohydrin, NEt_3, CH_2Cl_2, 20°C.

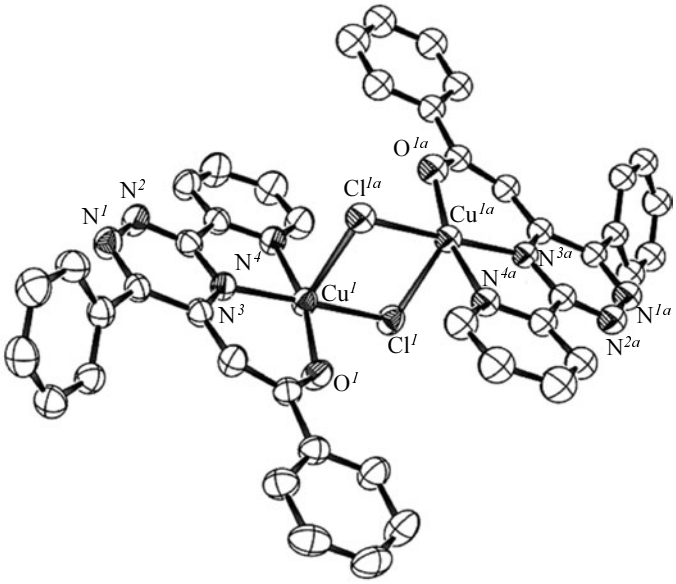
The elemental analyses of compounds **Ia–Ig** obtained are in agreement with the calculated data, and in the mass spectra the peak of the molecular ion is observed. In solution the compounds apparently exist as 5-(2-R-2-hydroxyethenyl)-1,2,4-triazines **A** which is evidenced by the presence in the ^{1}H NMR spectrum of a broadened one-proton singlet in the downfield region (15 ppm) and of a one-proton singlet of a methine proton at 6.2 ppm, and also by the absence in the IR spectrum of compound **Ie** of the absorption band from the stretching vibrations of the carbonyl group. On the other hand we cannot totally exclude the existence of the third form, 5-acylmethylene-4*H*-1,2,4-triazines **C**. Form **B** is excluded for the ^{1}H NMR spectrum lacks a two-proton singlet from the methylene gtoup.

In any event whatever the form of existence the anions of triazines **I** behave as N,N,O-ligands and efficiently chelate Cu(II). For instance, triazine **Ia** reacts with copper(II) chloride dihydrate in acetonitrile forming complex **VI**. We succeeded in obtaining single crystals of complex **VI** and therefore we were able to study it by means of FAB mass spectrometry and X-ray diffraction analysis. The neutral complex **VI** obtained is a centrosymmetrical dimer (see the figure). The chelating part of the ligand (pyridine and triazine rings, and also carbonylmethylene fragment) is exactly planar. The Cu(II) atom in the complex **VI** is pentacoordinate, the coordination sites form a square pyramid with the N, N, O atoms and a bridging Cl in the base of the pyramid, and the other bridging Cl in its vertex. The distance between the copper atoms in the dimer is 3.442 Å, exceeding the sum of the van der Waals radii (2.7 Å). Besides the structure of complex **VI** contains two very long Cu–Cl bonds (2.7173 Å) exceeding the sum of the atomic radii of Cu(II) and Cl^- (2.54 Å).

Thus the data obtained in the present study suggest that the 5-acylmethyl-3-pyridyl-1,2,4-triazines are of interest as accessible efficient ligands for transition metals.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker WM-250 (250 MHz), solvent DMCO-d_6–CCl_4, 1:1, internal reference TMS Mass spectra were measured on Varian MAT-311A instrument, ionization by electron



Structure of complex **VI** according to X-ray diffraction study. Lengths of some bonds (A): Cu^1–Cl^1 2.252, Cu^1–N^4 2.041, Cu^1–N^3 1.954, Cu^1–O^1 1.937, Cu^1–Cl^{1a} 2.717, Cu^1–Cu^{1a} 3.442.

beam. IR spectra were obtained on Fourier IR spectrometer Perkin Elmer Spectrum I. Cyanotriazine **V** was prepared by known procedure [15].

Synthesis of 1,2,4-triazines I. In 5 ml of anhydrous THF was dispersed 1.2 mmol of sodium hydride, then 1.4 mmol of acetophenone or trifluoroacetone was added. In 20 min the dispersion obtained was poured to a dispersion of 1 mmol of 1,2,4-triazine 4-oxide **II** in 20 ml of THF cooled to –20°C, and the mixture was stirred for 3 h. Then 1.2 mmol of acetic acid was added, the solvent was removed at a reduced pressure, and the residue was extracted with toluene. On distilling off toluene from the extract the residue was treated with acetonitrile; the arising bright-yellow precipitate was filtered off and recrystallized from toluene.

3-(2-Pyridyl)-5-phenacyl-6-phenyl-1,2,4-triazine (Ia). Yield 0.3 g (85%), mp 155–156°C. ^{1}H NMR spectrum, δ, ppm: 6.25 s (1H, COCH), 7.48–7.80 m (11H), 8.14 m (1H, Py), 8.54 m (1H, Py), 8.95 m (1H, Py), 15.39 br.s (1H, NH). Found, %: C 74.79; H 4.47; N 15.86. $C_{22}H_{16}N_4O$. Calculated, %: C 74.98; H 4.58; N 15.90.

3-(2-Pyridyl)-6-phenyl-5-(4-chlorophenacyl)-1,2,4-triazine (Ib). Yield 0.3 g (80%), mp 151–152°C. ^{1}H NMR spectrum, δ, ppm: 6.21 s (1H, COCH), 7.45–7.79 m ($10H_{arom}$), 8.12 m (1H, Py), 8.53 m (1H, Py), 8.89 m (1H, Py), 15.42 br.s (1H, NH). Found, %: C 74.79; H 4.47; N 15.86. $C_{22}H_{15}ClN_4O$. Calculated, %: C 68.31; H 3.91; N 14.48.

5-(4-Methylphenacyl)-3-(2-pyridyl)-6-phenyl-1,2,4-triazine (Ic). Yield 0.27 g (75%), mp 147–148°C. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 6.21 s (1H, COCH), 7.19–7.73 m ($10H_{arom}$), 8.06 m (1H, Py), 8.51 m (1H, Py), 8.89 m (1H, Py), 15.34 br.s (1H, NH). Found, %: C 75.59; H 4.97; N 15.26. $C_{23}H_{18}N_4O$. Calculated, %: C 75.39; H 4.95; N 15.29.

3-(2-Pyridyl)-6-phenyl-5-(4-fluorophenacyl)-1,2,4-triazine (Id). Yield 0.13 g (50%), mp 216–218°C. IR spectrum (KBr), cm^{-1}: 559, 681, 697, 803, 875, 1113, 1137, 1190, 1213, 1409, 1564, 3064, 3084. ^{1}H NMR spectrum, δ, ppm: 6.45 s (1H, COCH), 7.01–8.15 m (10H), 8.56 m (1H, Py), 8.81 m (1H, Py), 8.89 m (1H, Py), 15.34 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 344 (14) $[M]^+$. Found, %: C 71.12; H 4.07; N 15.20. $C_{22}H_{15}FN_4O$. Calculated, %: C 71.34; H 4.08; N 15.13.

3-(2-Pyridyl)-5-trifluoroacetylmethyl-6-phenyl-1,2,4-triazine (Ie). Yield 0.25 g (70%), mp 214–215°C. ^{1}H NMR spectrum, δ, ppm: 5.78 s (1H, COCH), 7.61–7.78 m (5H, Ph), 7.80 m (1H, Py), 8.17 m (1H, Py), 8.59 m (1H, Py), 8.90 m (1H, Py), 14.50–15.50 br.s (1H, NH). Found, %: C 59.31; H 3.22; N 16.27. $C_{17}H_{11}F_3N_4O$. Calculated, %: C 59.31; H 3.22; N 16.27.

6-(4-Methoxyphenyl)-3-(2-pyridyl)-5-trifluoroacetylmethyl-1,2,4-triazine (If). Yield 0.14 g (60%), mp 236–238°C. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H, CH_3), 5.76 s (1H, COCH), 7.70–7.81 m (4H, Ph), 7.82 m (1H, Py), 8.21 m (1H, Py), 8.57 m (1H, Py), 8.89 m (1H, Py), 14.50-15.50 br.s (1H, NH). Found, %: C 57.58; H 3.61; N 14.97. $C_{18}H_{13}F_3N_4O_2$. Calculated, %: C 57.76; H 3.50; N 14.97.

3-(2-Pyridyl)-5-trifluoroacetylmethyl-6-(4-chlorophenyl)-1,2,4-triazine (Ig). Yield 0.25 g (50%), mp 241–243°C. ^{1}H NMR spectrum, δ, ppm: 5.80 s (1H, COCH), 7.69–7.79 m (4H, Ph), 7.82 m (1H, Py), 8.33 m (1H, Py), 8.59 m (1H, Py), 8.90 m (1H, Py), 14.50–15.50 br.s (1H, NH). Found, %: C 53.99; H 3.00; N 14.75. $C_{18}H_{13}F_3N_4O_2$. Calculated, %: C 53.91; H 2.66; N 14.79.

Synthesis of complex VI. To a solution of 26 mg (0.15 mmol) of copper(II) chloride dihydrate in 30 ml of acetonitrile was added at stirring at room temperature a solution of 53 mg (0.15 mmol) of ligand **Ia** in 30 ml of acetonitrile. The mixture obtained was left standing for 3 days at slow evaporation of the solvent. The separated crystals were filtered off. Yield 0.114 g (80%). Mass spectrum FAB, *m/z* (I_{rel}, %): 417 $[Cu(\mathbf{Ia})]^+$. Found, %: C 58.31; H 3.52; N 12.27. $C_{44}H_{30}Cl_2Cu_2N_8O_2$. Calculated, %: C 58.54; H 3.57; N 12.41.

X-ray diffraction analysis was carried out on a diffractometer Nonius Cad-4, MoK_α radiation, graphite monochromator (ω-scanning), 293 K. The structure was solved by the direct method SIR-97 and refined by the least-squares procedure SHELXL-97. $C_{44}H_{30}Cl_2Cu_2N_8O_2$. *M* 900.74, *a* 9.145(4), *b* 9.804(4), *c* 12.096(7) Å, α 66.03(4), β 76.65(4), γ 88.03(4)°, *V* 962.0(8) Å^3, *Z* 1, D_{calc} 1.555 g/cm^3, μ 1.295 cm^{-1}. Space group *P-1(bar)*. Number of measured reflections 5311. Number of reflections with $I > 2\sigma(I)$ 5213. *R* 0.0377. The structure of complex **VI** and the length values of some bonds are given on the figure.

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