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Dual Mechanism of Enamine–enamine Rearrangement of 1,3-diaryl-3-(1-imidazolyl)propen-2-ones

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Abstract—The formation of 1,3-diaryl-3-(1-imidazolyl)propen-1,3-diol that is an intermediate of enamine–enamine rearrangement of 1,3-diaryl-3-(1-imidazolyl)propen-1-ones constitutes the key stage of the dual mechanism of the rearrangement proper. The reaction of 1,3-diaryl-2,3-dibromopropan-1-ones with a primary amine provides 1,3-diaryl-3-iminopropan-1-ones as a result of enamine–imine prototropic rearrangement.

The condensation of α,β-dibromoketones with secondary amines (1,2,4-triazole, imidazole, piperidine, diethylamine, diethanolamine) in DMSO, DMF, or dioxane is a general procedure for preparation of aminochalcones [1–4]. The reaction is commonly carried out at tenfold molar excess of amine to ensure complete consumption of dibromoketone and to provide a possibility of products isolation without use of chromatography. At the condensation in excess of liquid amine that serves also as solvent the latter is easily recovered by distillation from the reaction mixture. The hydrolysis of 1,3-diketones with piperidino or diethylamino groups to carbonyl compounds and secondary amines (in dilute acetate buffer and in perchloric acid) [5], in future presumably with overheated steam, is of special interest for preparation of monoheteryl- and diheteryl 1,3-diketones that can find application as complexing agents in the chemistry of radioactive elements, as is applied thenoyltrifluoroacetone.

The reaction of 2,3-dibromo-1-(2,4-dichlorophenyl-3-(4-nitrophenyl)propan-1-one with imidazole afforded a mixture of isomeric enamines **I** and **VI** [3]. Therewith compound **I** can be converted into compound **VI**. In [3] a unique mechanism was proposed for this enamine–enamine rearrangement (**I**) → (**VI**) occurring at 20°C in DMSO and at –20°C in frozen DMSO within 24– 240 h or at 140–160°C without solvent occurring within 20 min. The presumed mechanism included intermediates **III** and **IV** (Scheme 1).

When the reaction mixture is frozen in 30 seconds after mixing the reagents and then is maintained at –39÷–40°C for 120 h the single product of condensation is obtained, compound **I**. At 20°C within 4 h in solutions in DMSO containing only compound **I** or **VI** no changes were observed. The heating of these solutions to 140–160°C for 20 min resulted in formation of a mixture of enamines **I** and **VI** with the latter prevailing. Similar transformation was previously observed without solvent. However at temperature lowered to 120–125°C neither of the enamines suffers isomerization.

The results of these experiments can be understood in assumption that in the solution or in frozen DMSO operates an alternative concerted rearrangement mechanism. The rearrangement is catalyzed by a complex of imidazolium ion **VII** with imidazole **VIII** that effects a proton transfer from a nitrogen atom of heterocycle to the oxygen atom of CO group. This complex is indispensable not only for occurrence of 1,3-migration of the imidazole ring but also for transformation of C=O group into a tertiary alcohol group. Simultaneously the arising in the process imidazolide anion **IX** effects deprotonation of intermediate **II**. Because of high concentration of the catalyst and of rearrangement mechanism intermediate **IV** forms at high rate. This is evidenced by formation of enamines **I** and **VI** mixture within 30 min at 20°C [3].

The described condensation is carried out also with the primary amines. For instance, reaction of 2,3-dibromo-1,3-diphenylpropan-1-one (**X**) with cyclohexylamine (**XI**) in solution or in frozen DMSO apparently gives rise to enamine **XII** as intermediate that undergoes a prototropic rearrangement to afford 1,3-diphenyl-3-cyclohexyliminopropen-1-one (XIII) (Scheme 2).

It follows from the above reasoning that in reaction of chalcone dibromide with sodium imidazolide in

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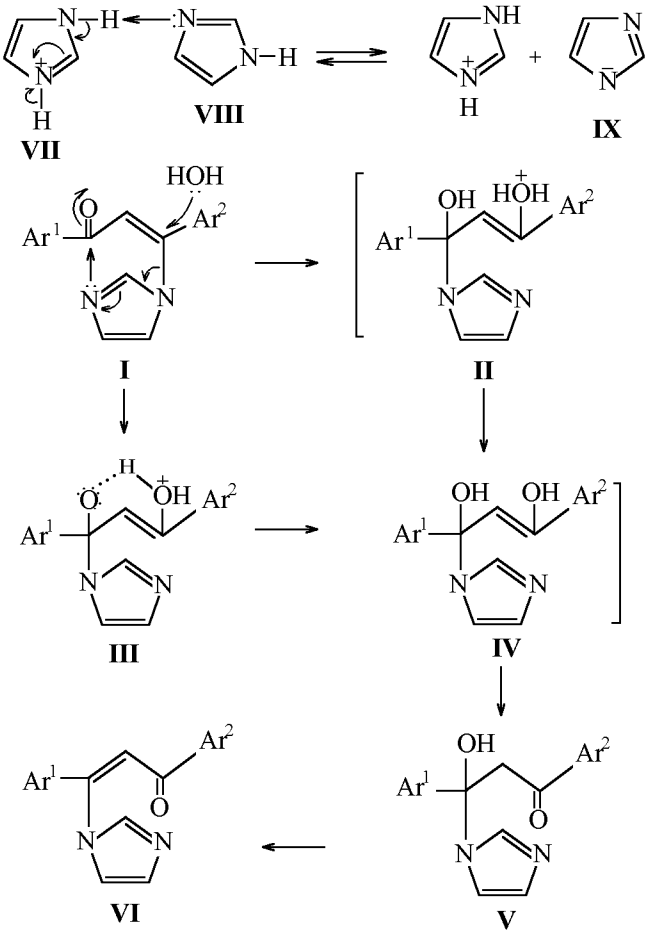
Scheme 1.



Ar^1 = 2,4-$Cl_2C_6H_3$, Ar^2 = 4-$O_2NC_6H_4$.

anhydrous DMSO the expected product would be enamine **I**, and in aqueous DMSO where would operate the catalytic system imidazolium cation **VII**–imidazole **VIII**, 1 : 4, each isomer **I** or **VI** would be converted in their equilibrium mixture whose composition depends on the temperature of the process.

EXPERIMENTAL

Melting points were measured on Boëtius device and are reported uncorrected. Mass spectra were registered on mass spectrometer MKh-1320 with direct injection of sample into the ion source; ion source temperature 60 °C, ionizing electrons energy 70 eV, emission current 50 μA. DMSO used in the synthesis was commercial product of "chemically pure" grade, cyclhexylamine and piperidine were distilled just before use.

The temperature dependence of equilibrium ratio of compounds **I** and **VI** was performed by means of TLC on Silufol plates in the system benzene–acetone, 2 : 1 [R_f 0.73 (**I**), 0.62 (**VI**)]. Visual estimation of components was based on intensity of spots; as reference were used solutions of both compounds of equal concentration.

3-Piperidino-1,3-diphenylpropen-1-one. Under conditions preventing access of CO_2 were thoroughly mixed 19.4 g (0.05 mol) of 2,3-dibromo-1,3-diphenylpropan-1-one (**X**) and 42.5 g (0.5 mol) of piperidine. The mixture was either maintained at 20°C for 5 days or heated to 80°C for 16 h. The consumption of dibromide **X** was monitored by TLC in systems benzene and benzene–acetone, 4 : 1 (development in iodine vapor). Piperidine was distilled off, the residue was diluted with 150 ml of water, and the reaction product was extracted into benzene (6 × 100 ml). Combined extracts were washed with water (3 × 70 ml), dried on Na_2SO_4 and evaporated to dryness. Yield 67%, mp 3–34°C (from a mixture benzene–hexane, 1 : 1). Found, %: C 82.15; H 7.01; N 5.13. $C_{20}H_{21}NO$. Calculated, %: C 82.43; H 7.26; N 4.80.

1,3-Diphenyl-3-cyclohexylaminopropen-1-one (XIII). A solution of 3.68 g (0.01 mol) of dibromide **X** and 9.9 g (0.1 mol) of cyclohexylamine in 40 ml of DMSO was stirred for 30 s, then was frozen and either maintained for 120 h at –30÷–40°C or 72 h at 20°C. On dilution of the reaction mixture with water (360 ml) the workup was done as above. Yield 60%, mp 52–54°C (from a mixture benzene–hexane, 2 : 1). Mass spectrum, *m/z*: 305 $M^{+\cdot}$, 200, 105.

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