Copper(II)-catalyzed Molecular Rearrangements: the Behaviour of Arylhydrazones of some 3-Benzoylazoles in the Presence of Copper(II) Acetate

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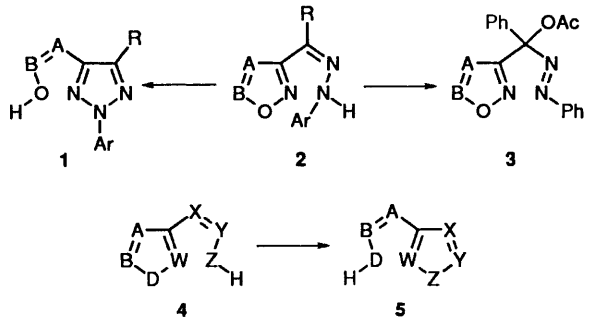
The reactivity of arylhydrazones of some 3-benzoylazoles (1,2,4-oxadiazole, isoxazole and 1,2,5-oxadiazole) induced by copper(II) catalysis has been investigated. In the 1,2,4-oxadiazole and isoxazole systems, copper(II) acetate monohydrate in methanol effectively induces molecular rearrangements of the arylhydrazones into the corresponding 1,2,3-triazoles, that is, without competitive oxidation processes. In the 1,2,5-oxadiazole series, no ring transformation occurs by the action of the same salt, the expected rearrangement into triazole oximes being achieved rather with sodium ethoxide in ethanol.

Molecular rearrangements of the arylhydrazones of 3-acylazoles **2** into the corresponding 1,2,3-triazoles **1** constitute well known and widely investigated processes within the Boulton–Katritzky scheme,[1] currently named 'mononuclear heterocyclic rearrangements'.[2] These represent special cases of ring transformations of five-membered heterocycles with a participating three-atom side chain (**4** ⟶ **5**) which have been comprehensively reviewed.[3,4] Rearrangements of the arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles[5] and 3-benzoylisoxazole[6] have also been investigated in a detailed kinetic approach, and a generalized mechanism has been proposed, emphasizing the role of (*a*) the nucleophilicity of the attacking nitrogen in the side chain, (*b*) the acidity of the N–H group of the arylhydrazono moiety (in a base-catalysed pathway), (*c*) the electrophilicity of N-2 ring nitrogen and (*d*) the nucleofugacity of the leaving group.[5,6] The reactivity of the phenylhydrazones of 3-benzoylazoles (**2**; R = Ar = Ph) towards lead tetraacetate has been also explored:[7] here, similarly to what is generally observed for ketone arylhydrazones,[8] the expected oxidative process yielded the azoacetates **3**.



Scheme 1

Our interest in molecular rearrangements of five-membered heterocycles containing a three-atom side chain has led us to analyze the behaviour of some 3-benzoylazole arylhydrazones towards copper(II) ions, which can act both as oxidants and as complexing agents. The reactivity of a hydrazone or a hydrazone-like group towards oxidizing metal salts has been extensively investigated[9] under various experimental conditions, and a variety of results have been observed. In the case of Cu^{II} salts, besides hydrolysis to give a carbonyl group,[10] the involvement of Cu^{II} in redox processes has been emphasized.[11] Here, we report preliminary results concerning the reactivity of arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **6**, 3-benzoyl-5-phenylisoxazole **7**, and 3-benzoyl-4-methyl-1,2,5-oxadiazole **13**.

Results and Discussion

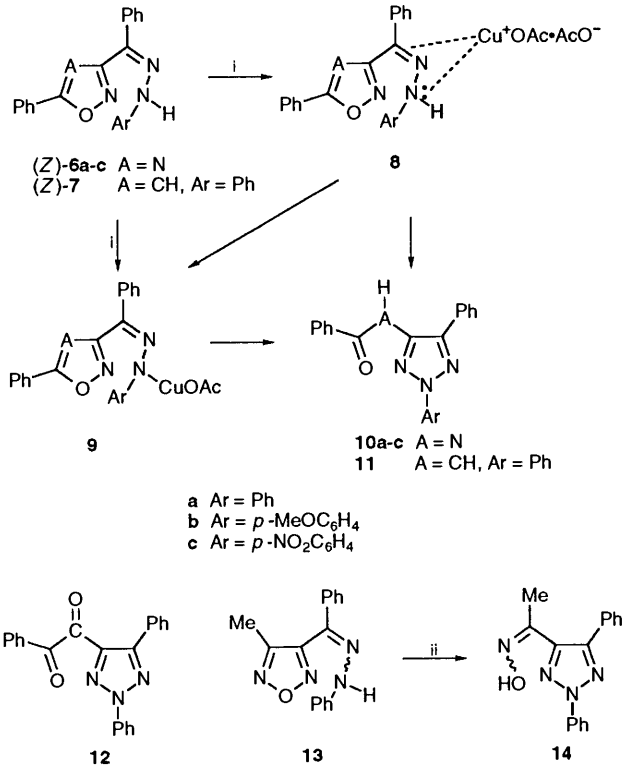
3-Benzoyl-5-phenyl-1,2,4-oxadiazole Arylhydrazones.—When treated with either equimolar or catalytic amounts of copper(II) acetate monohydrate in methanol at room temperature, 3-benzoyl-5-phenyl-1,2,4-oxadiazole phenylhydrazone (*Z*)-**6a** readily underwent a simple molecular rearrangement into the 4-benzoylamino-1,2,3-triazole **10a**, without accompanying oxidative processes. It is worth remembering that, in the absence of Cu^{II} ions, (*Z*)-**6a** rearranges into **10a** upon melting[12] or when subjected to base catalysis.[5a,c,d] On the other hand, control experiments showed that, in methanol, the acetate anion alone (from sodium acetate) does not induce the ring rearrangement. Furthermore, the observed copper-promoted reaction fails to occur in acetic acid or in methanol containing acetic acid. Finally, as far as the influence of substituents in the phenyl ring of the phenylhydrazono moiety is concerned, we qualitatively observed that the reactivity is increased by the electron-donating *para*-methoxy group, and decreased by the electron-withdrawing *para*-nitro substituent.

Copper(II) acetate also catalyzes the configurational isomerization of the arylhydrazono group: thus, the (*E*)-**6a** isomer undergoes the same Cu^{II}-catalyzed rearrangement, without appreciable differences in reactivity. In the absence of Cu^{II} ions, (*E*)-**6a** isomerizes and then rearranges into **10a** only upon melting[13] or by an amine-catalyzed reaction,[14] whereas it remains unchanged in refluxing ethanol. Moreover, acetic acid equilibrates the two configurational isomers, but does not induce the ring rearrangement.[13]

Although a detailed mechanistic investigation is in progress, some comments are possible. On the basis that, overall, a non-oxidative process occurs, it is reasonable to suppose that the reaction involves a transient complex between copper acetate and the substrate; complexation involving the imino double bond and the lone-pair of the amino nitrogen of the side chain **8** (A = N) would then seem a likely path for the rearrangement to follow, leading to the new N–N bond, in which the acetate anion induces the required proton transfer. The reaction could also proceed *via* a sigma-bonded copper-hydrazone intermediate such as **9** (A = N). Here, whatever the nature of the N–Cu bond, enhanced nucleophilicity of the attacking nitrogen would result. On the other hand, the configurational isomerization could be explained in terms of the ability of

copper ions to behave as a Lewis acid towards the imino double bond or the imino nitrogen lone-pair. A path for the rearrangement, involving the behaviour of Cu^{II} ions as oxidants[11,15] towards the hydrazono moiety, may be rejected on the basis of some EPR experiments which excluded the intermediacy of radical cations.

In order to ascertain the role of acetate anions we studied the behaviour of (*Z*)-**6a** with Cu^{II} sulfate in methanol at room temperature. Surprisingly, no rearrangement occurred: however, addition of sodium acetate or triethylamine to a mixture of (*Z*)-**6a** and equimolar or even catalytic amounts of copper sulfate, gave ready formation of **10a**, pointing to an essential role for either species as a base or ligand component. On the other hand, it has been verified that in methanol at room temperature neither sodium acetate nor triethylamine induced rearrangement in the absence of Cu^{II} ions.



Scheme 2 *Reagents and conditions:* i, $Cu(OAc)_2 \cdot H_2O$, MeOH; ii, EtONa, EtOH, reflux

3-Benzoyl-5-phenylisoxazole Phenylhydrazones.—The expected rearrangement of both (*E*)- and (*Z*)-phenylhydrazones **7** into the phenacyltriazole **11** readily occurred when the compound was heated with copper acetate in refluxing methanol for a few minutes. Here again, catalytic amounts of copper acetate are active in promoting a reaction which, in the absence of such salt, requires base catalysis.[6,16] As expected, Cu^{II} sulfate in refluxing methanol, although performing the configurational equilibration, failed to induce the rearrangement; this, however, was accomplished by the introduction of sodium acetate to the mixture.

The catalyzed rearrangement was always accompanied by the formation of **12** which could, in principle, arise from the oxidation[17] of the initially formed phenacyltriazole **11**. However, control experiments suggest that compound **12** derives rather from a parallel reaction. Studying the behaviour of the (*Z*)-phenylhydrazone **7** with Cu^{II} acetate in methanol at room temperature, we found that in the presence of equimolar amounts of the copper salt, besides significant hydrolysis of the hydrazono group, (*Z*)-**7** slowly furnished **12** as the predominant product. On the other hand, when catalytic amounts of the Cu^{II} salt coupled with an excess of sodium acetate were used, the same substrate rapidly rearranged into the phenacyltriazole **11** as the main product, thus confirming the driving role of the acetate ion in the rearrangement.

3-Benzoyl-4-methyl-1,2,5-oxadiazole Phenylhydrazones.—At variance with the results obtained for the 1,2,4-oxadiazole and isoxazole series, (*E*)- or (*Z*)-3-benzoyl-4-methyl-1,2,5-oxadiazole phenylhydrazones **13** failed to undergo copper(II)-catalyzed rearrangement into the expected triazole oximes **14**, only configurational isomerization of the hydrazono moiety being observed. This behaviour clearly results from the lower reactivity of the 1,2,5-oxadiazole heterocycle towards rearrangements involving the side-chains.[2,4] We then explored the reactivity of **13** towards the usual base-induced rearrangement. Here we found that both (*E*)- and (*Z*)-**13** readily rearranged when heated with sodium ethoxide in refluxing ethanol without any significant difference in reactivity. As expected, the reaction gave a mixture of (*E*)- and (*Z*)-oximes **14**, from which pure isomers could be obtained.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. IR spectra (Nujol mulls) were recorded on a Perkin-Elmer 257 instrument, ^1H NMR (250 MHz) and ^{13}C NMR (62 MHz) spectra on a Bruker 250/52 spectrometer (tetramethylsilane as internal standard). HPLC analyses were performed with a Perkin-Elmer Series 10 instrument, by using a C-18 SIL-X-10 Perkin-Elmer column, eluting with water–acetonitrile (9 : 1 v/v), and monitoring the absorbance at $\lambda = 254$ nm.

Compounds **6a–c**,[5b,12,13] **7**,[16] **10a–c**,[5b,12] **11**,[16] and **13**[7] were prepared as reported. Copper(II) acetate monohydrate, copper(II) sulfate pentahydrate, and methanol (anhydrous grade) were available from the Aldrich Company. TLC was performed by using Merck aluminium sheets with silica gel 60 F_{254} and mixtures of light petroleum–ethyl acetate as eluent. Column chromatography was carried out on Merck silica gel (0.040–0.063 mm), eluting with light petroleum–ethyl acetate mixtures.

3-Benzoyl-5-phenyl-1,2,4-oxadiazole Arylhydrazones.—To a suspension of the phenylhydrazone (*Z*)-**6a** (0.25 g, 0.75 mmol) in methanol (50 cm^3) copper acetate (0.15 g, 0.75 mmol) was added, and the mixture was stirred at room temperature for 2 h. Removal of the solvent and work-up with water gave **10a** in almost quantitative yield. Similar results were obtained by using catalytic amounts (0.1 mol equiv.) of copper acetate or with the (*E*)-**6a** isomer.

Under similar experimental conditions, (*Z*)-**6b** rearranged into **10b** within 1 h, whereas (*Z*)-**6c** rearranged into **10c** within 12 h. The higher reactivity of (*Z*)-**6b** with respect to (*Z*)-**6a** in dilute methanol solutions was also monitored by HPLC analysis.

3-Benzoyl-5-phenylisoxazole Phenylhydrazones.—To a boiling solution of the phenylhydrazone (*Z*)-**7** (0.25 g, 0.75 mmol) in methanol (50 cm^3), copper acetate (0.15 g, 0.75 mmol) was added, and the mixture was gently refluxed for 1–2 min. HPLC analysis showed the formation of **11** (90%) and **12** (10%). The solvent was removed under reduced pressure and the residue treated with water and extracted with diethyl ether. The extract was dried and evaporated and the chromatography of the residue separated **11** (0.15 g) and **12** (0.015 g), m.p. 130 °C (from light petroleum) (Found: C, 74.6; H, 4.2; N, 12.0. $C_{22}H_{15}N_3O_2$ requires C, 74.78; H, 4.28; N, 11.89%); ν_{max}/cm^{-1} 1660 and 1680 (C=O); $\delta_H(CDCl_3)$ 7.4–7.7 (m, 9 H, ArH), 8.0–8.15 (m, 4 H, ArH), and 8.2–8.3 (m, 2 H, ArH); $\delta_C(CDCl_3)$ 119.5–151.2 (3 Ph and hetero ring), 188.4 and 192.8 (2 C, 2 C=O).

Similar results were obtained by using catalytic amounts (0.1 mol equiv.) of copper acetate or with the (*E*)-**7** isomer. In a control experiment, **11** was refluxed for 2 h with equimolar amounts of copper acetate in methanol: HPLC analysis showed the formation of **12** (5%).

A methanol solution containing equimolar proportions of copper acetate and (*Z*)-**7** when stored for 8 days at room temperature gave a 50% yield of **12**, together with decomposition products, some **11** and 3-benzoyl-5-phenylisoxazole.[18] In contrast, a methanol solution (50 cm^3) containing sodium acetate (0.1 g), a catalytic amount of copper acetate (0.01 g) and (*Z*)-**7** (0.25 g), after 20 h at room temperature gave **11** (75%), **12** (20%) and 3-benzoyl-5-phenylisoxazole (5%) (by HPLC).

3-Benzoyl-4-methyl-1,2,5-oxadiazole Phenylhydrazones.—A mixture of the hydrazone (*Z*)-**13** (0.21 g, 0.75 mmol) and copper acetate (0.15 g, 0.75 mmol) in methanol (50 cm^3) was refluxed for 1 h. TLC analysis showed the occurrence of the (*Z*) $\rightleftharpoons$ (*E*) configurational equilibration,[7] whereas the rearranged oximes **14** were absent. Compound (*E*)-**13** behaved similarly.

Compound (*Z*)-**13** or (*E*)-**13** (1 g) was refluxed for 6 h in ethanol (50 cm^3) containing sodium ethoxide (from 0.25 g of sodium). After removal of the solvent, work-up with water and neutralization with acetic acid gave a crude mixture of both oxime isomers **14**. Column chromatography gave at first (*Z*)-**14** (0.1 g), m.p. 140 °C (from ethanol) (Found: C, 69.1; H, 5.2; N, 20.0. $C_{16}H_{14}N_4O$ requires C, 69.05; H, 5.07; N, 20.13%); ν_{max}/cm^{-1} 3240–3280 (OH); $\delta_H(CDCl_3)$ 2.38 (s, 3 H, Me), 7.35–7.55 (m, 6 H, ArH), 7.70 (s, 1 H, OH) and 7.80–8.20 (2 m, 4 H, ArH); δ_H(DMSO) 11.54 (OH); $\delta_C(CDCl_3)$ 13.32 (Me).

Further elution gave (*E*)-**14** (0.8 g), m.p. 119 °C (from aqueous ethanol) (Found: C, 69.2; H, 5.1; N, 20.2. $C_{16}H_{14}N_4O$ requires C, 69.05; H, 5.07; N, 20.13%); ν_{max}/cm^{-1} 3180–3200 (OH); $\delta_H(CDCl_3)$ 2.30 (s, 3 H, Me), 7.35–8.17 (3 m, 10 H, 2 Ph) and 8.83 (s, 1 H, OH); δ_H(DMSO) 11.12 (OH); $\delta_C(CDCl_3)$ 20.76 (Me). (The assignment of configuration is based on the δ values of Me signals in the ^{13}C NMR spectra[19] and on the expected higher stability of the (*E*)-isomer in aryl methyl ketoximes).[20]

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