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Base or Copper Promoted Annulation Reactions of α-Aminohydrazones.

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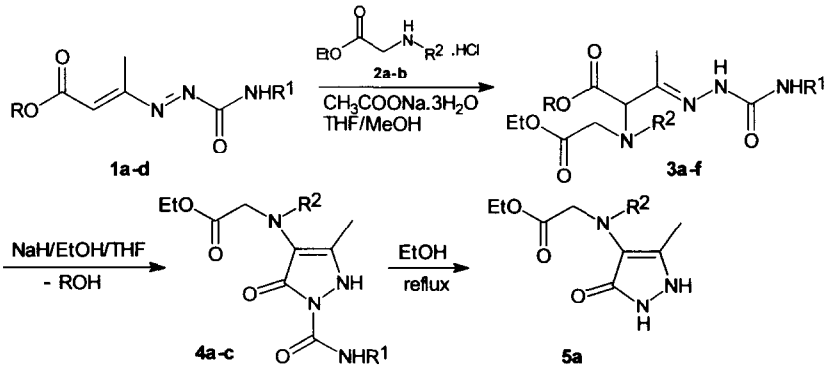
Abstract: The title compounds, obtained by 1,4-addition of sarcosine or glycine ethyl ester on conjugated azoalkenes, gave the 1-ureido-4-amino-3-methyl-1*H*-pyrazol-5(2*H*)-ones through a base promoted heterocyclization process, while in the presence of copper (I) species the 1-ureido-5-methyl-4-imidazolines and the 4-methoxycarbonyl-5-methyl-1-ureidoimidazole were obtained. The mechanism of these reactions is discussed. © 1997 Published by Elsevier Science Ltd.

The presence of the azo group in the heterodiene system of conjugated azoalkenes favours nucleophilic attack producing hydrazone derivatives by 1,4-conjugated addition. These compounds have been shown to represent useful building blocks for the construction of a variety of polyfunctionalized heterocyclic pyrroles, thiazoles and pyrazoles.[1]

In connection with our ongoing interest in developing new synthetic strategies for the construction of five-membered heterocyclic rings involving conjugated azoalkenes and transition metals,[2] we report that α-aminohydrazones **3a-f**, obtained in excellent yields by the reaction between 4-alkoxycarbonylazoalkenes **1a-d** and the N-methyl-glycine **2a** and the glycine **2b** ethyl esters,[3] can undergo base promoted heterocyclization reactions at room temperature to produce the 1-ureido-1*H*-pyrazol-5(2*H*)-ones **4a-c** (Scheme 1, Table). Smooth solvolytic cleavage of the group linked to the nitrogen atom in position 1 of **4a** led to the 1-unsubstituted- 1*H*-pyrazol-5(2*H*)-one **5a** in 66% yield[4] (Scheme 1).

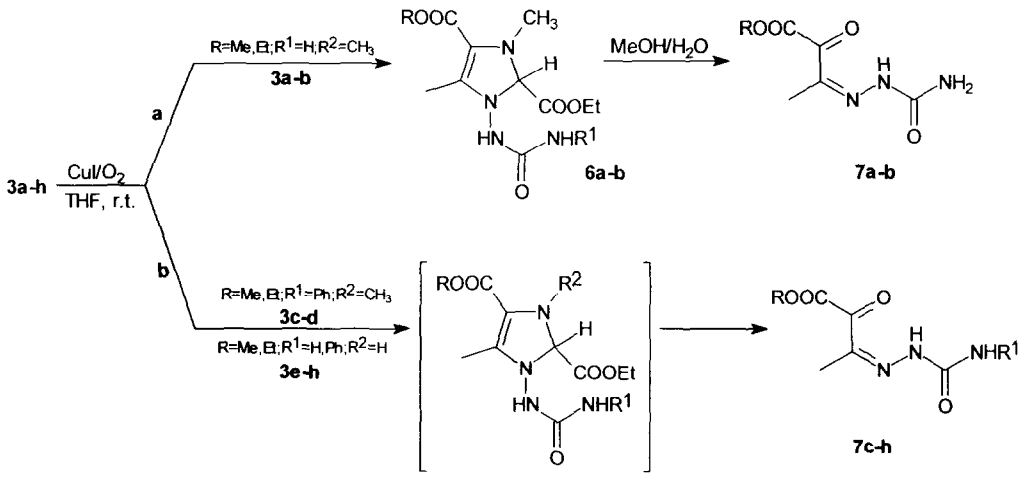


Scheme 1

Table Synthesis of α-Aminohydrazones **3** and 1-Ureido-1*H*-pyrazol-5(2*H*)-ones **4**

Entry	R	R^1	R^2	Recovered **3** (% yield)	Recovered **4** (% yield)
1	Me	H	Me	**3a** (91)	**4a** (83)
2	Et	H	Me	**3b** (82)	**4a** (85)
3	Me	Ph	Me	**3c** (80)	**4b** (93)
4	Et	Ph	Me	**3d** (68)	**4b** (89)
5	Me	H	H	**3e** (88)	
6	Et	H	H	**3f** (70)	
7	Me	Ph	H	**3g** (90)	**4c** (81)
8	Et	Ph	H	**3h** (78)	**4c** (85)

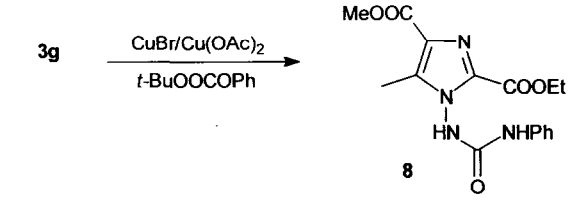
Moreover, the same derivatives **3a-h** can undergo a novel copper promoted reaction to give 1-ureido-4-imidazolines **6a-b** or the α-ketohydrazones **7a-f** (Scheme 2). The α-aminohydrazones **3a-b** in the presence of a stoichiometric amount of copper iodide gave, by precipitation, the 1,4-alkoxycarbonyl-5-methyl-1-ureido-4-imidazolines **6a-b** in THF, under oxygen atmosphere, in good yields (78% of **6a** and 83% of **6b**). They were easily collected by filtration[5] (Scheme2, path a). The above reactions performed with a catalytic amount of copper iodide resulted in the isolation of the same reaction products in poor yields.



Scheme 2

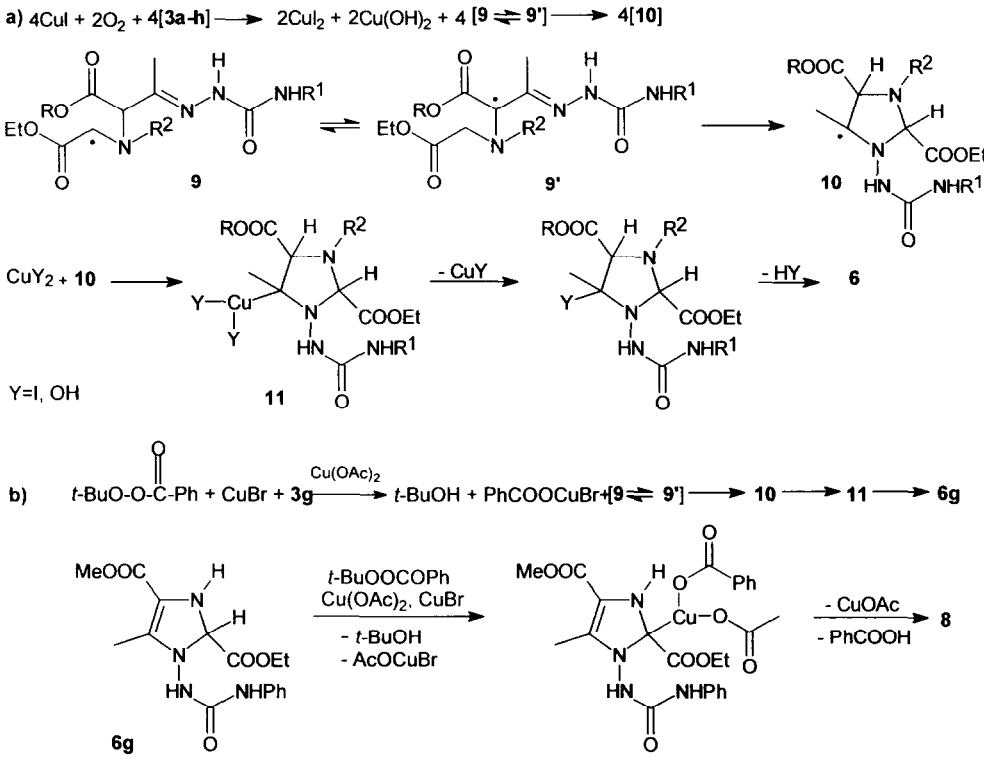
With the α-aminohydrazones **3c-d** (Scheme 2, path b) no precipitation occurred during the course of the reactions and usual work up of the crude resulted in the isolation of the α-ketohydrazones **7c-d** in quantitative yields. However, the ^{1}H-NMR analysis of the crude, by simple evaporation of the tetrahydrofuran, showed a signal pattern which can be undoubtedly attributed to the 4-imidazolines **6**. To shed further light on this point, **6a-b** were reacted in MeOH/H_2O leading to the formation of **7a-b** in quantitative yields[6]. Finally, the α-aminohydrazones **3e-h** gave the α-ketohydrazones **7e-h** (Scheme2, path b). However in this case the yields were moderate (about 40%) and the ^{1}H-NMR analysis of the crude showed a more complex signal pattern. In order to achieve a better understanding of these results and widen the scope of this synthetic methodology, we performed the copper promoted reaction of α-aminohydrazone **3g** in a stronger oxidizing medium with the aim to favour the aromatization of the corresponding 4-imidazoline intermediate **6g** to a more stable

imidazole. Indeed, both cyclization and aromatization reactions were carried out in one step starting from **3g** to give **8** (53% yield) by a copper-mediated peroxide process introduced some years ago by Kharash and Sosnovsky[7] and widely used as an alternative method to oxidize a variety of dihydroheterocyclic compounds to their dehydro derivatives[8] (Scheme 3).



Scheme 3

The proposed mechanism for the formation of the 4-imidazolines **6** and imidazole **8** is depicted in Scheme 4.



Scheme 4

The results can be rationalized according to the following sequence (Scheme 4a): a) formation of (Cu^{III}-$O^{\cdot}$ ⇔ $Cu^{II}O^{\cdot}$), as postulated in several works[9] dealing with the oxidations of different compounds by the copper(I)/oxygen system, b) homolytic cleavage of CH bonds giving rise to stabilized radical intermediates[10] **9** and **9'** arising from the selective cleavage by chelation of the α-hydrogen atoms of α-aminocarboxylic esters[11] present in the molecule; c) formation of **10** via regioselective intramolecular attack on the carbon-nitrogen

double bond; d) generation of the σ-copper (III) complex **11** by oxidative addition of Cu(II) species; e) reductive elimination regenerating copper (I) species; e) β-elimination reaction providing the 4-imidazolines **6**. Similarly the formation of imidazole **8** (Scheme 4b) is believed to involve the same sequential copper promoted reactions to give the corresonding imidazolidine **11**, from which 4-imidazoline **6g** is obtained by loss of copper (I) acetate and benzoic acid. Further, *t*-butyloxy radical promoted oxidation of compound **6g** would then produce the imidazole **8.**

In conclusion the base promoted reactions of easily accessible α-aminohydrazones represent a simple and efficent method for the preparation of both 1-substituted and 1-unsubstituted 4-amino-1*H*-pyrazol-5(2*H*)-ones. Moreover, the copper promoted reactions of the same α-aminohydrazones provide a new facile regiocontrolled synthesis of the imidazole ring system. Further work is in progress in order to evaluate the scope and limitations of these reactions, and in particular our efforts are toward the optimization of the reaction conditions with the use of catalytic amounts of copper salts.

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5. A typical procedure for the synthesis of compounds **6** is as follows: to a solution of **3a** (0.3 g, 1.04 mmol) in anhydrous tetrahydrofuran (5 ml) was added copper iodide (0.19 g, 1.04 mmol) under an oxygen atmosphere. The mixture was stirred at room temperature for 1h and the precipitate, collected by filtration under vacuum, was then crystallized from ethyl acetate/petroleun ether giving 0.232g (78% yield) of **6a**. ^{1}H-NMR δ 5.55 (s, 1H, NH), 5.70-4.60 (bs, 2H, NH_2), 4.42 (s, 1H, H-2), 4.20 (q, 2H, CH_2), 3.88 (s, 3H, OCH_3), 2.83 (s, 3H, NCH_3), 1.91 (s, 3H, CH_3), 1.27 (t, 3H, CH_3); EI-MS m/e (relative intensity): 285 ($M-1^+$, 14), 229 (98), 186 (100), 126 (95), 100 (55).
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