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Tetrahedron Letters 46 (2005) 4457–4459
Tetrahedron Letters

# Unexpected results in the heterocyclization of 5-acetylenylpyrazole-4-carboxylic acid hydrazides under the influence of CuCl: formation of a diazepinone and dehydrodimerization into the corresponding bis(pyrazolo[4,3-*d*][1,2]diazepinone)

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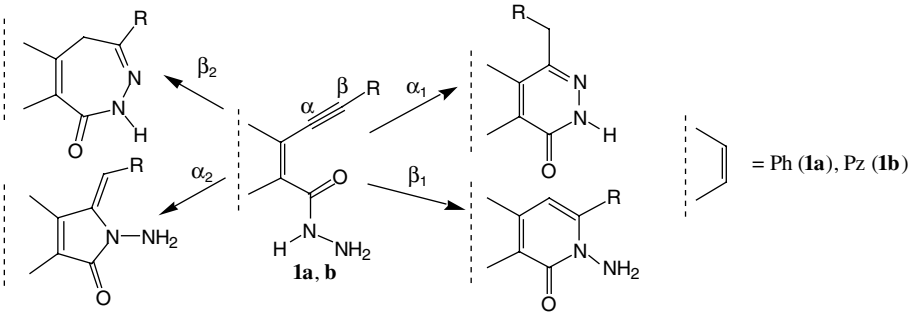
Received 1 February 2005; revised 27 April 2005; accepted 27 April 2005

**Abstract**—The simple reaction of cyclization of hydrazides of *vic*-acetylenylbenzoic and acetylenylpyrazole carboxylic acid can lead to four different compounds: five-membered *N*-aminolactams, six-membered *N*-aminolactams, six-membered diazinones and diazepinones, but only the first three have been described. In this paper we report the unexpected formation of a bis(pyrazolo[4,3-*d*][1,2]diazepinone, the structure of which has been established by X-ray crystallography.


## 1. Introduction

In previous reports, we have described that the intramolecular cyclization of hydrazides of *vic*-acetylenylbenzoic and acetylenylpyrazole carboxylic acid **1** occurs through three different paths.[1,2] Benzene derivatives **1a** underwent cyclization into five-membered *N*-aminolactams under the influence of a base (path $\alpha_2$ Scheme 1, KOH in boiling ethanol), while pyrazole derivatives **1b** gave only six-membered *N*-aminolactam rings in the same




**Scheme 1.** The four possible routes of cyclization of hydrazides derived from acetylenylbenzoic (**1a**) and pyrazolecarboxylic (**1b**) acids.

*Keywords*: Pyrazolopyridines; Cross-coupling; Hetarylacetylenes; Heterocyclization.
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doi:10.1016/j.tetlet.2005.04.127

conditions (path $\beta_1$). Isomerization of benzene derivatives **1a** under the action of copper(I) chloride in boiling dimethylformamide afforded only the corresponding condensed six-membered diazinones.[1] Isomerization of pyrazole derivatives **1b** led both to diazinones and to *N*-aminopyridones (paths: $\alpha_1$ and $\beta_1$, Scheme 1).[1,2]

Thus, only three compounds out of the four possible cyclization products have been reported whereas formation of the diazepinone ring (path $\beta_2$) has never been observed.

## 2. Results and discussion

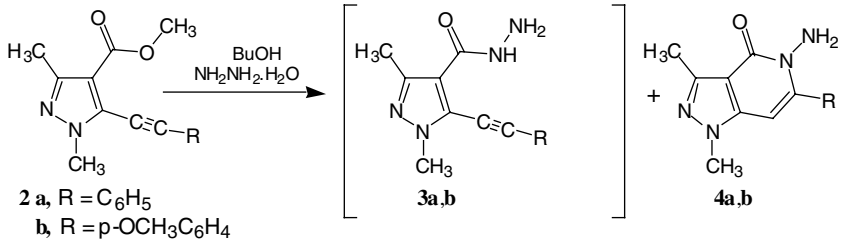
Taking into account that the nucleophilicity of the triple bond depends markedly on its position on the pyrazole ring, and that this can affect the course of the cyclization,[2–4] we have continued our study of hydrazides exploring the behavior of those derived from 5-acetylenylpyrazole-4-carboxylic acid methyl ester (**2a**). This isomer is characterized by the presence of the acetylenic group in the lowest electron density 5-position and the acyl hydrazide in the highest electron density 4-position.

We have found that the hydrazinolysis of 1,3-dimethyl-5-(phenylethynyl)pyrazole-4-carboxylic acid methyl ester (**2a**), even under the conditions of hydrazide preparation (boiling 11 h with 80% hydrazine hydrate in butanol) led to the cyclization product **4a** (*N*-aminopyridone) in 52% yield (Scheme 2). On the other hand, the hydrazinolysis (15 h) of 1,3-dimethyl-5-(*p*-methoxyphenyl)ethynylpyrazole-4-carboxylic acid methyl ester (**2b**), afforded a mixture of the desired hydrazide **3b** (yield 33%)[5] and the cyclization product (*N*-aminopyridone) **4b** (yield 37%) (as a consequence of the higher nucleophilicity of the 5 position in the pyrazole ring) (Scheme 2). The decrease in the yield of lactam **4b** can be a consequence of the +M-effect of the methoxy group. Increasing the reaction time up to 30–35 h provided only *N*-aminolactam **4b** (yield 65%). However, the best route to prepare **4b** (70% yield) is to boil hydrazide **3b** in the presence of potassium hydroxide in ethanol.[6] An unexpected result was obtained when hydrazide **3b** was used in a reaction of heterocyclization in the presence of CuCl. Thus, hydrazide **3b** in the presence of CuCl in boiling dimethylformamide led to a bis(pyrazolo[4,3-*d*][1,2]diazepinone **5b** (50% yield).[7] Cyclization of 1,3-dimethyl-5-(*p*-methoxyphenyl)ethynylpyrazole-4-carboxylic acid hydrazide (**3b**) occurred in a different way and for the first time, we have found the fourth possibility of Scheme 1 (path $\beta_2$): the formation of a diazepinone ring. Moreover, we have found that the final product has the structure of a dehydrodimer (**5b**, Scheme 3).

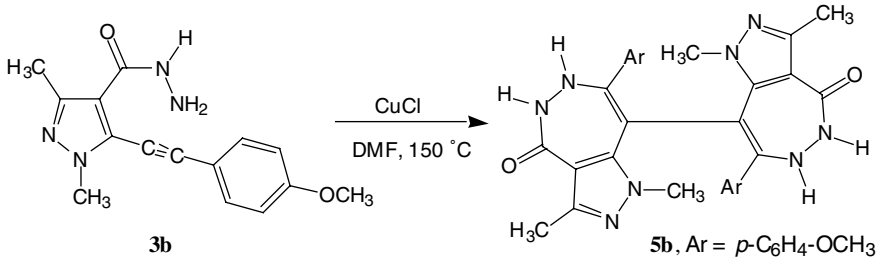
Pyrazolo[4,3-*d*][1,2]diazepines are seldom found in the literature, amongst the rare examples are two compounds prepared by cycloaddition on 1,2-diazepines.[8] The mechanism of formation of **5b** is still unknown but it probably involves a copper-mediated oxidative coupling. The structure of **5b** was established according to the analytical and spectral data as well as from the X-ray analysis (Fig. 1).[9]

Values of the corresponding bond lengths in the two **5b** molecules are practically the same. The seven-membered cycles have the 'bath'-conformation. Crystal packing is formed by intermolecular hydrogen bonds. The starting acetylenylpyrazole derivatives were obtained by coupling the methyl ester of 1,3-dimethyl-5-iodopyrazole-4-carboxylic acid with the corresponding copper(I) acetylides in boiling dimethylformamide under argon atmosphere. Yields of derivatives **2a** and **b** are 60–70%.

In conclusion all four possibilities of Scheme 1 of the hydrazides **1b** have been observed. The direction of the




**Scheme 2.** Hydrazinolysis of methyl esters **2a** and **b**.




**Scheme 3.** The unexpected formation of the pyrazolodiazepinone **5b**.

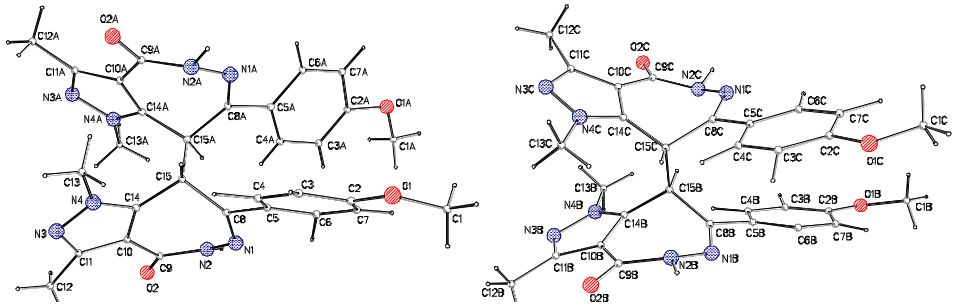


**Figure 1.** View of two crystallographically independent molecules of **5b** and numbering scheme.

reaction depends on the mutual arrangement of the acetylene and the acylhydrazino groups, the nature of the substituent attached to the acetylenic fragment and the condensation conditions.

## Acknowledgement

This work was supported by CRDF (NO-008-XI).

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5. Full spectroscopic and analytical data have been obtained for all the compounds reported herein. For example, hydrazide of 1,3-dimethyl-5-(*p*-methoxyphenyl)ethynylpyrazole-4-carboxylic acid methyl ester (**3b**): IR, $\nu$/cm$^{-1}$ (KBr): 2210 (C≡C); 1648 (C=O); 3250, 3435 (NH, $NH_2$). $^1$H NMR, $\delta_H$ (DMSO-$d_6$): 2.27 (s, 3H, $CCH_3$); 3.80 (s, 3H, $NCH_3$); 3.83 (s, 3H, $OCH_3$); 4.11 (s, 2H, $NH_2$); 6,99 [*Ph*$OCH_3$: m, 2H, H (2,6)]; 7.84 [*Ph*$OCH_3$: m, 2H, H (3,5)]; 10.45 (s, 1H, NH).
6. Experimental procedure for the cycloisomerization of hydrazides in the presence of potassium hydroxide: hydrazide of pyrazole carboxylic acid **3b**, 0.2 g (0.7 mmol) and 0.1 g of KOH were boiled in 5 mL of ethanol for 2 h (TLC control: Silufol). The solvent was distilled under reduced pressure, the precipitate was dissolved in benzene and filtered through alumina (1.5 × 1 cm), then the benzene was distilled under reduced pressure. The product was crystallized from ethanol, yield **4b** 0.14 g (70.0%), mp 213–215 °C (EtOH), IR, $\nu$/cm$^{-1}$ (KBr): 1679 (C=O); 3436 ($NH_2$); $^1$H NMR, $\delta_H$ ($CDCl_3$): 2.41 (s, 3H, $CH_3$); 3.72 (s, 3H, $NCH_3$); 3.87 (s, 3H, $OCH_3$); 4.67 (s, 2H, $NH_2$); 6,96 [*Ph*$OCH_3$: m, 2H, H (2,6)]; 8.00 [*Ph*$OCH_3$: m, 2H, H (3,5)]; 7.34 [s, 1H, H(7)].
7. Experimental procedure for the cycloisomerization of hydrazides in the presence of copper(I) chloride for example: hydrazide (**3b**), 0.3 g (1.0 mmol), 0.08 g of copper(I) chloride in 5 mL of dimethylformamide were boiled 4 h under argon atmosphere. The reaction mixture was cooled and poured into chloroform and was washed with aqueous ammonium hydroxide. The chloroform solution was dried over sodium sulfate and filtered through alumina (0.5 × 1 cm), and the solvent was evaporated under reduced pressure. The product was crystallized from ethanol, yield **5b** 0.15 g (50.0%), mp. 350–350.5 °C (EtOH). IR, $\nu$/cm$^{-1}$(KBr): 1662 (C=O); 3439 (NH); $^{13}$C–$^1$H NMR, $\delta_H$ (DMSO-$d_6$): 2.30 (s, 6H, $CH_3$, $^3J_{8H-8H'}$ = 10.3 Hz; $^1J_{C-H}$ = 136.6 Hz); 3.39 (s, 6H, $NCH_3$); 3.78 (s, 6H, $OCH_3$); 5.58 [s, 2H, H(8)]; 6.93 [*Ph*$OCH_3$: m, 4H, H (3,5)]; 7.54 [*Ph*$OCH_3$: m, 4H, H (2,6)]; 11.19 (s, 2H, 5-NH); $\delta_C$ (DMSO-$d_6$): 12.84 (q, $CH_3$); 34.28 [d, $C_8$, $^1J^{13}$C-H(8) = 136.6 Hz, $^2J^{13}$C-H(8′) = 5.9 Hz]; 35.26 (q, $NCH_3$); 55.26 (q, $OCH_3$); 111.02 (s, $C_{3a}$); 114.11 (d, $C_m$); 128.37 (d, $C_o$); 128.69 (s, $C_i$); 138.25 (s, $C_{8a}$); 148.99 (s, $C_3$); 150.46 (s, $C_7$); 160.84 (s, $C_p$); 161.86 (s, $C_4$). The values for the $^3J_{HH}$ constants for 8-H were obtained from the splitting of the $^{13}$CH satellites for this signal in the $^1$H NMR spectrum, and so was the value $^1J_{13C-1H}$ = 136.6 Hz. Attribution of the signals in the $^{13}$C NMR spectrum were made on the basis of the information obtained from the mono-resonance and 2D correlation spectra $^{13}$C–$^1$H at direct and remote spin–spin coupling constants. Anal. Calcd for $C_{30}H_{30}N_8O_4$: C, 63.59; H, 5.34; N, 19.78. Found: C, 62.89; H, 5.32; N, 19.53.
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9. Crystal data for **5b**: $C_{30}H_{30}N_8O_4$, *FW* = 566.62, crystals are monoclinic, $P2_1$, $a$ = 8.029(5), $b$ = 25.916(14), $c$ = 14.222(9) Å, $\beta$ = 101.147(12)°, $V$ = 2904(3) Å$^3$, $Z$ = 4, $D_{calcd}$ = 1.296 g/cm$^{-3}$, $\mu$ = 0.090 mm$^{-1}$, total of 9441 ($\theta_{max}$ = 23.31°), 7538 unique ($R_{int}$ = 0.0795), 2654 ($F > 4\sigma_F$), 870 parameters. Goof = 0.704, $R1$ = 0.0572, $wR2$ = 0.0842 ($I > 2\sigma_I$), $R1$ = 0.1635, $wR2$ = 0.1086 (all data), largest diff. peak 0.141 e Å$^{-3}$. CCDC 254372 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK. Fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk.