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UNEXPECTED CYCLIZATION ROUTE FOR *o*-ETHYNYLBENZOIC ACIDS HYDRAZIDES IN THE PRESENCE OF BASE*

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The reaction of o-ethynylbenzoic acids hydrazides with base has been studied. In the presence of a strong donor substituent (1,5-dimethylpyrazol-4-yl) it has been found that an unusual cyclization route occurs to give the corresponding benzopyridazinone instead of the expected isoindolinone.

Keywords: arylacetylenes, benzopyridazinones, ethynylbenzoic acids esters, isoindolinones, heterocyclization, cross coupling, reactions with hydrazine.

The high synthetic potential of polyfunctional aryl- and hetarylacetylenes ensures the unabated interest of chemists in this class of compound. Vicinal functionally substituted aryl- and hetarylacetylenes are very convenient synthons in the preparation of condensed heterocycles which are promising biologically active compounds [1].

In fact, a study of the reactivity of vicinal hydrazides of acetylenylbenzoic and pyrazolylcarboxylic acids has shown that the presence of the α- and β-carbon atoms of the triple bond and the two nucleophilic centers ("amine" and "amide" nitrogen atoms) in the hydrazide group guarantee many outcomes for their reactions [2, 3]. Recent investigations of the heterocyclization of *vic*-acetylenylpyrazolecarboxylic acid hydrazides led to the unexpected result that oxidative coupling of the molecule occurs along with formation of a condensed diazepinone ring (which, in itself, was seen for the first time) [4].

In addition, the very limited number of previous investigations of aromatic series compounds does not reveal the full picture of even the basic dependence of the heterocyclization route for unsaturated hydrazides. Study of the cyclization of the *vic*-acetylenylbenzoic acid hydrazides series is limited to just two examples [2, 3]. This circumstance, together with the marked effect of the nature of the substituent at the triple bond carbon atom on the reaction course [4], led us to broaden the range of acetylenyl substituents in a series of *ortho*-acetylenylbenzoic acids hydrazides.

The synthesis of the starting *o*-acetylenylbenzoates **1a,b** was carried out by treating methyl *o*-iodobenzoate with the corresponding terminal alkynes under copper-palladium catalysis conditions [5] using the system ($Pd(PPh_3)_2Cl_2$, CuI, NEt_3) in 67-97% product yield.

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* Dedicated to Academician B. A. Trofimov in his 70th jubilee.

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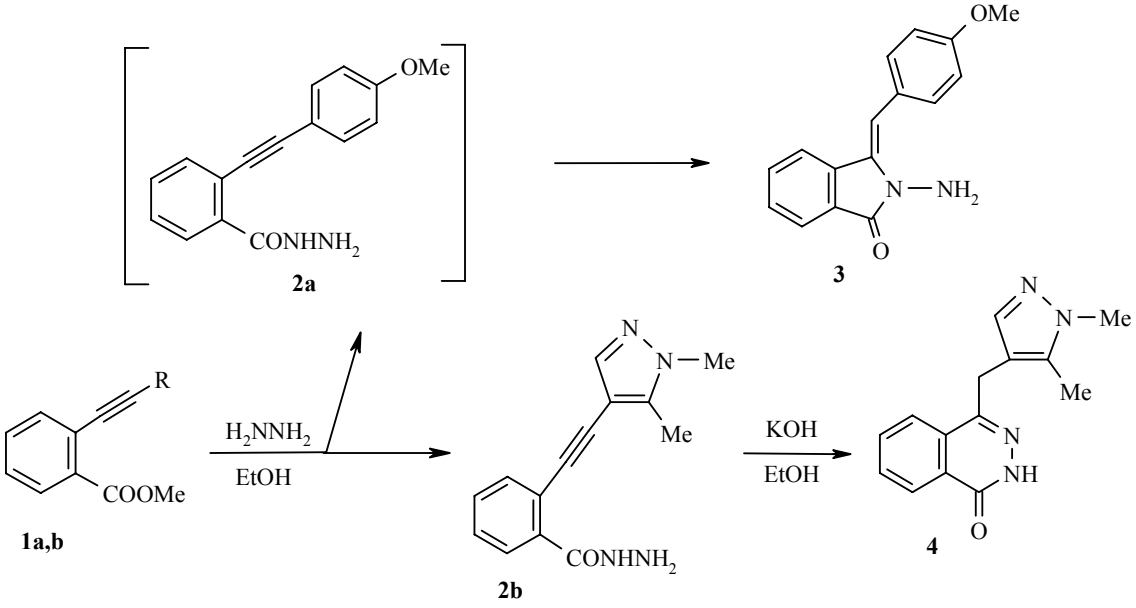
Treatment of the ethynylbenzoates **1a,b** with hydrazine hydrate in ethanol showed significant differences in both reactivity and reaction path.



1,2 a R = *p*-$MeOC_6H_4$, **b** R = 1,5-dimethylpyrazol-4-yl

Heating the (*p*-methoxyphenyl)ethynylbenzoate **1a** with hydrazine hydrate in ethanol did not stop at the stage of intermediate formation of hydrazide **2a** but immediately gave the cyclization product **3** in 67% yield. Support for a 5- rather than a 6-membered N-aminolactam was based on the different values of the CO stretching vibrations in the IR spectra of these isomers [6]. It is known that increased strain on going from the 6- to the 5-membered ring brings about an increase in ν_{CO} by 30-35 cm^{-1}. In known δ-lactams the stretching vibrational frequency for the CO group (ν_{CO}) is 1660-1680 cm^{-1} while in γ-lactams it is not less than 1695-1700 cm^{-1}. The value of ν_{CO} in the IR spectrum of compound **3** of 1706 cm^{-1} fully agrees with the assignment of an amino-substituted γ-lactam structure for **3**.

In the case of a 4-pyrazolyl residue (having a strong +M-effect) the intermediate acetylenylhydrazide **2b** (85%) was separated. If the former formation of the N-aminolactam **3** is in agreement with our previous data [2, 3] then formation of the open form (hydrazide **2b**) in high yield and without traces of the proposed N-aminolactam is observed for the first time.

Since the hydrazide **2b** appears to be inert towards hydrazine the cyclization was carried out by selecting the more powerful base of KOH in alcohol. The result of the reaction proved unexpected, the main product being the benzopyridazinone **4** in 70% yield. It should be noted that acetylenic derivatives of benzoic and pyrazolecarboxylic acid hydrazides gave only the γ- and δ-N-aminolactams in the presence of hydrazine hydrate or KOH base, i.e. attack of the amide nitrogen atom always occurs at a triple bond carbon atom. Such a route fully agrees with that expected since the reaction is carried out with a strong base, in fact the attacking agent is the N-anion formed from the amide fragment of the hydrazide group.

In addition, according to our data [2, 3], the formation of a diazinone ring (as in the case of compound **4**) for both benzene and pyrazole derivatives occurs only in neutral media in the presence of CuI, i.e. when the amine nitrogen atom is a stronger nucleophiles than the amide nitrogen atom. The novelty of the reaction reported in this work relates to the formal formation of the benzopyridazinone **4** as the product of attack of the α-carbon atom of the triple bond by the amine nitrogen atom (a less powerful nucleophile than the N-anion) in the presence of KOH with subsequent prototropic isomerization. It is likely that the formation of the diazinone occurs *via* a rearrangement. The mechanism of this reaction is currently being studied by quantum-chemical methods.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker AV-300 instrument (300 MHz) using $CDCl_3$ with TMS as internal standard and IR spectra on a Vector 22 instrument as a film (compound **1b**) or as KBr tablets (compounds **2b, 3, 4**). Melting points were measured on a Koffler stage. High resolution mass spectra were taken on a Finnigan MAT 8200 instrument (EI, 70 eV). Elemental analysis was performed on a Carlo Erba (Italy) model 1106 CHN analyzer. Commercially available $PdCl_2(PPh_3)_2$ and 2-methyl-3-butyn-2-ol were obtained from the Aldrich company.

Methyl 2-[(1,5-dimethyl-1H-pyrazol-4-yl)ethynyl]benzoate (1b). Methyl *o*-iodobenzoate (1.31 g, 5 mmol), CuI (0.01 g, 0.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.02 g, 0.06 mmol), PPh_3 (0.04 g, 0.3 mmol), triethylamine (3.0 ml, 4.35 g, 43 mmol), and (1,5-dimethyl-4-pyrazolyl)acetylene (0.72 g, 6 mmol) were added successively with stirring to benzene (30 ml) in a stream of argon. The mixture was held under an argon stream for 5 h 40 min at 80ºC. Monitoring of the reaction was carried out by TLC (chloroform). At the end of the reaction the mixture was cooled to 25ºC, filtered through a layer of aluminium oxide (20×20 mm) and SiO_2 (10×20 mm), washed initially with benzene (2×5 ml) and then ethyl acetate (3×5 ml), and the solvent was distilled off. The product was dried in a desiccator over KOH to give the product **1b** (1.51 g, 97%) with n_D^{20} 1.6195. IR spectrum, ν, cm^{-1}: 1728.4 (C=O), 2209.6 (C≡C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.46 (3H, s, CH_3); 3.82 (3H, s, NCH_3); 3.94 (3H, s, OCH_3); 7.32 (1H, t, *J* = 7.5, H-5); 7.52 (1H, t, *J* = 6.2, H-4); 7.58-7.59 (2H, m, H-3, $H_{pyrazole}$); 7.94 (1H, d, *J* = 7.9, H-6). Mass spectrum, *m/z*: 254.1049 [M]. $C_{15}H_{14}N_2O_2$. Calculated M 254.1046. Found, %: C 71.22; H 5.53; N 11.22. $C_{15}H_{14}N_2O_2$. Calculated, %: C 70.85; H 5.55; N 11.02.

Methyl 2-[(4-methoxyphenyl)ethynyl]benzoate (1a) was prepared similarly to **1a**, yield 2.5 g (95%), mp 65-67ºC (hexane) (mp 67-69ºC [7]).

2-[(1,5-Dimethyl-1H-pyrazol-4-yl)ethynyl]benzohydrazide (2b). Hydrazine hydrate (80%, 0.21 g, 4.2 mmol) was added to a solution of ester **1b** (0.72 g, 2.8 mmol) in ethanol (5 ml) and was refluxed for 8 h 35 min (TLC monitoring). The mixture was cooled to 25ºC and the precipitate formed was filtered off and recrystallized from ethyl acetate (7 ml) to give the product (0.61 g, 85%) with mp 109-110ºC. IR spectrum, ν, cm^{-1}: 1641.2 (C=O), 2204.2 (C≡C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3); 2.72 (2H, s, NH_2); 3.81 (3H, s, NCH_3); 7.35-7.55 (3H, m, H-3,4,5$_{arom}$); 7.58 (1H, s, $H_{pyrazole}$); 7.98 (1H, d, *J* = 8.0, H-6); 8.53 (1H, s, NH). Mass spectrum, *m/z*: 254.1157 [M]. $C_{14}H_{14}N_4O$. Calculated: M 254.1167. Found, %: C 66.62; H 5.75; N 10.37. $C_{14}H_{14}N_4O_2$. Calculated, %: C 66.13; H 5.55; N 22.02.

2-Amino-3-(4'-methoxybenzylidene)isoindolin-1-one (3). Hydrazine hydrate (80%, 0.4 g, 10 mmol) was added to a solution of ester **1a** (1 g, 3.8 mmol) in ethanol (5 ml) and was refluxed for 14 h 50 min (monitoring by TLC, CH_2Cl_2–AcOEt, 1:1). The mixture was cooled to 25ºC and the precipitate formed was filtered off and recrystallized from ethanol (25 ml) to give the product **3** (0.67 g, 67%) with mp 140-141ºC. IR spectrum, ν, cm^{-1}: 1641.2 (C=O), 2204.2 (C≡C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, OCH_3); 4.35 (2H, s, NH_2); 6.65 (1H, s, =CH); 6.85 (2H, d, *J* = 8.7, H *o*,*o*'-Ph); 7.65 (2H, d, *J* = 8.7, H *m*, *m*'-Ph); 7.65-7.84 (4H, m, H-4,5,6,7). Mass spectrum, *m/z* 266.1048 [M]. $C_{16}H_{14}N_2O_2$. Calculated: M 266.1050. Found, %: C 72.05; H 5.46; N 10.52. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.16; H 5.30; N 10.52.

4-[(1,5-Dimethyl-1H-pyrazol-4-yl)methyl]phthalazin-1(2H)-one (4) KOH (60 mg, 110 mmol) was added to a solution of hydrazide **2b** (100 mg, 39 mmol) in ethanol (5 ml) and the product was refluxed for 15 h (monitoring by TLC, AcOEt). The mixture was cooled to 25ºC and the precipitate formed was filtered off and recrystallized from ethanol to give the product **4** (70 mg, 70%) with mp 236-238ºC. IR spectrum, ν, cm^{-1}: 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.21 (3H, s, CH_3); 3.73 (3H, s, NCH_3); 4.03 (2H, s, CH_2); 7.70-7.85 (4H, m, H-5,6,7,8); 9.93 (1H, s, NH). Mass spectrum, *m/z*: 254.1155 [M]. $C_{14}H_{14}N_4O$. Calculated: M 254.1167. Found, %: C 66.42; H 5.63; N 22.23. $C_{14}H_{14}N_4O$. Calculated, %: C 66.13; H 5.55; N 22.20.

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