Study of the Heterocyclization of *vic*-Substituted Hydrazides of Acetylenylpyrazolecarboxylic Acids into *N*-Amino Pyrazolopyridinones

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We report a new and efficient methodology to prepare *N*-amino pyrazolo[4,3-*c*]pyridin-4-ones **4** and *N*-amino pyrazolo[3,4-*c*]pyridin-4-ones **8** from *vic*-acetylenyl/hydrazido pyrazoles. The procedure involves the intermediate synthesis of methyl esters of acetylenyl-pyrazole carboxylic acids and the subsequent cyclization under a variety of conditions.

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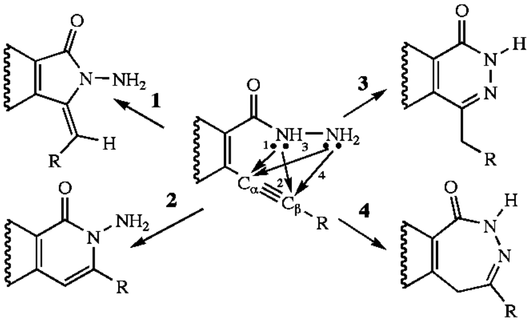
The synthesis and the reactivity of vicinally substituted functional acetylenylarenes and -hetarenes, in particular, the study of their heterocyclization is an actual and rapidly developing field of organic chemistry. Besides, the resulting condensed heterocycles, which are difficult to obtain by other methods, have recently become increasingly important [1-6]. An added interest is to discover rules for the direction of the addition of a functional group to a triple bond, which are hampered by the absence of a wide arsenal of substrates with regularly varying structural, electronic and steric parameters.

In the present paper we will explore the cyclization of hydrazides of *vic*-acetylenyl aromatic compounds. In Scheme 1, we have summarized the four possibilities: 1) Attack of the amido nitrogen atom to the α carbon of the triple bond to afford five-membered *N*-aminolactams (*N*-aminopyrrolidones). 2) Attack of the amido nitrogen atom to the β carbon of the triple bond to afford six-membered *N*-aminolactams (*N*-aminopyridones). 3) Attack of the amino nitrogen atom to the α carbon of the triple bond to afford six-membered diazinones (pyridazinones). 3) Attack of the amino nitrogen atom to the α carbon of the triple bond to afford seven-membered diazepinones.

Scheme 1



In an earlier paper [7], we have reported that the cyclocondensation of hydrazides of *vic*-acetylenylbenzoic and acetylenylpyrazolecarboxylic acids followed different pathways. Benzene derivatives, in the presence of bases, underwent cyclization into 5-membered *N*-aminolactams (type 1), while pyrazole derivatives gave only 6-membered *N*-aminolactams rings (type 2). Both benzene and pyrazole derivatives isomerize to the corresponding condensed pyridazinones (see type 3) under the action of copper(I) chloride in boiling dimethylformamide.

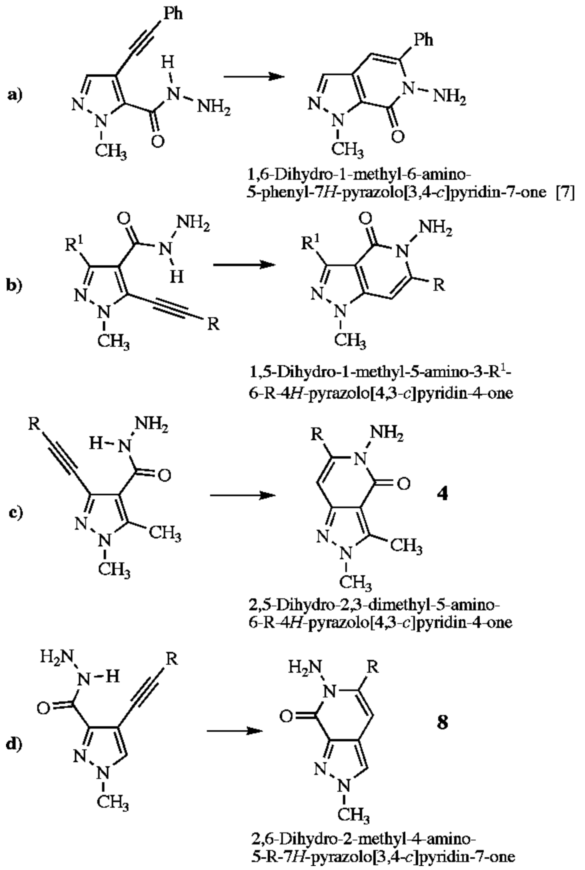
In the case of pyrazoles, depending on the relative positions of the hydrazide and the acetylene groups, four situations are possible (Scheme 2). The one we explored previously corresponds to case **a** [7], case **b** remains unknown and cases **c** and **d** will be the object of the present paper. In case **a** the reaction depends on the cyclization conditions: in basic medium (potassium hydroxide) the pyrazolo[3,4-*c*]pyridinone is obtained (class 2 of Scheme 1) but in neutral conditions (copper chloride in dimethylformamide), the pyridazinone (class 3 of Scheme 1) is isolated [7].

Results and Discussion.

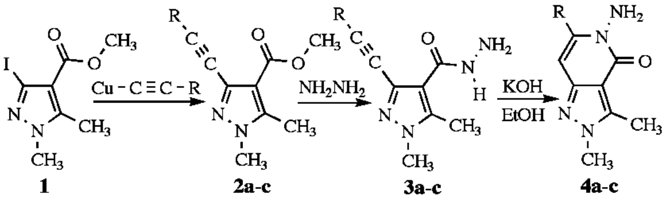
The nucleophilicity of the hydrazido group and the electrophilicity of the triple bond both depend markedly on their position in the pyrazole ring, and this can affect the course and ease of cyclization and even the possibility of whether the cyclization occurs [2,3,6]. Thus, we decided to perform a systematic study of the heterocyclization of compounds with two different arrangements of the interacting groups (acetylene and hydrazide) corresponding to cases **c** and **b** of Scheme 2. The synthetic results obtained are summarized in Tables 1-3.

The cyclization of hydrazides **3** carried out in ethanol in the presence of a base (potassium hydroxide) gave δ-*N*-aminolactams **4** in 50-90% yields (formally resulting from

Scheme 2

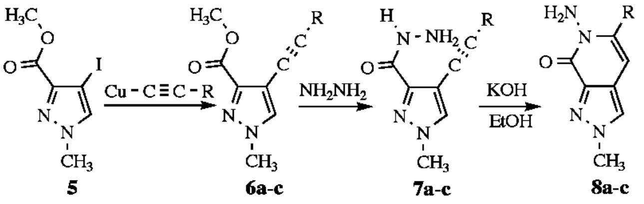


Scheme 3



R = C_6H_5 (**a**), R = *p*-$MeOC_6H_4$ (**b**), R = $CH_2OC_6H_5$ (**c**)

Scheme 4



R = C_6H_5 (**a**), R = *p*-$MeOC_6H_4$ (**b**), R = $CH_2OC_6H_5$ (**c**)

The synthesis of the starting iodopyrazoles (**1**,**5**) was described in references [8,9]. For preparing acetylenic esters we used Castro's method (copper acetylides) instead of Sonogashira cross-coupling (terminal acetylenes), because in the case of low reactive iodopyrazoles (especially 4-derivatives), Pd-Cu-catalyzed condensation of iodopyrazoles with terrminal acetylenes is accompanied by side-reactions, such as deiodination of pyrazolyl iodides and homo-coupling of terminal acetylenes [6].

Table 1

Ethynylpyrazolecarboxylic Acid Methyl Esters

Comp.	Time, hours	Yield, %	Mp ∞C (solvent)	Formula	Found Calculated % C	H	N	IR ν, cm^{-1} CƒC	C=O	^{1}H NMR (deuteriochloroform): δ
6a	5.5	80	154-155 [11] (EtOH)	$C_{14}H_{12}N_2O_2$	–	–	–	2235	1725	3.80, 3.88 (CO_2CH_3, N-CH_3), 7.60 (5-H), 7.2-7.4 m (Ph)
6b	5	66	123.5-124.5 (C_6H_6)	$C_{15}H_{14}N_2O_3$	66.65 66.49	5.20 5.01	10.36 10.02	2200	1715	4.02, 3.61, 3.87 (CO_2CH_3, N-CH_3, OCH_3), 7.64 (5-H), 6.8-7.5 m (C_6H_4)
6c	5	75	87.5-88.5 (hexane)	$C_{15}H_{14}N_2O_3$	66.65 67.06	5.22 5.23	10.35 9.89	2234	1721	3.88, 4.91 (CO_2CH_3, N-CH_3), 4.92 (CH_2), 7.51 (5-H), 6.9-7.3 m (Ph)
2a	6	65	93-94[11] (hexane)	$C_{15}H_{14}N_2O_2$	–	–	–	2235	1705	3.78, 3.88 (N-CH_3, OCH_3), 2.50 (5-CH_3), 7.4-7.8 m (Ph)
2b	8	60	129-130 (C_6H_6)	$C_{16}H_{16}N_2O_3$	67.59 67.86	5.67 5.62	9.85 9.75	2222	1716	3.82, 3.89, 3.81 (N-CH_3, OCH_3, CO_2CH_3), 2.55 (5-CH_3), 6.8-7.2 m (C_6H_4)
2c	5	80	65-66 (hexane)	$C_{16}H_{16}N_2O_3$	67.58 66.99	5.67 5.75	9.85 9.62	2235	1704	3.67, 3.76 (1-CH_3, CO_2CH_3), 4.92 (CH_2), 2.49 (5-CH_3), 6.9-7.3 m (Ph)

attack of the nitrogen amide atom on the β-carbon atom of the triple bond) (Scheme 3 and Table 3).

The cycloisomerization of hydrazides with the "opposite" arrangement of the triple bond and the hydrazide fragment in the cycle, **7**, occurs in a similar way (Scheme 4). The yields of d-*N*-aminolactams **8** were between 65 and 99% (Table 3).

Both 3-and 4-iodo derivatives underwent successful coupling with preformed copper acetylides in boiling dimethyl-formamide under argon atmosphere. The yields of the corresponding acetylenes **2a-c** and **6a-c** were 65-80% (Table 1). The hydrazides were prepared by heating the methyl esters of the corresponding carboxylic acids with an excess of hydrazine hydrate in butanol (10-12

Table 2

Hydrazides of Pyrazolecarboxylic Acids

Comp.	Time, hours	Yield, %	Mp ∞C (solvent)	Formula	Found Calculated % C	H	N	IR ν, cm^{-1} C∫C	C=O	NH_2 & NH	^{1}H NMR (deuteriochloroform): δ
7a	1	60	117-118 (C_6H_6)	$C_{13}H_{12}N_4O$	64.98 65.38	5.03 5.13	23.32 23.41	2214	1664	3460 3490	3.99 (N-CH_3), 7.65 (5-H), 6.7-7.6 m (Ph), 8.74 (NH), 5.74 (NH_2)
7b	1	50	193.5-194.5 (BuOH)	$C_{14}H_{14}N_4O_2$	62.21 62.47	5.21 5.26	20.73 20.39	2210	1653	3425 3460	3.87 (N-CH_3), 3.99 (OCH_3), 7.62 (5-H), 6.8-7.5 m (C_6H_4), 8.15 (NH), 4.07 (NH_2)
7c	3	81	80-81 (EtOH)	$C_{14}H_{14}N_4O_2$	62.21 62.18	5.22 5.28	20.73 20.77	2243	1673	3425 3440	3.97 (N-CH_3), 4.14 (CH_2), 7.29 (5-H), 6.9-7.0 m (Ph), 7.50 (NH), 4.92 (NH_2)
3a	12	50	179-180 (EtOH)	$C_{14}H_{14}N_4O$	66.12 65.80	5.55 5.53	22.04 21.58	2205	1650	3430 3475	3.71(N-CH_3), 2.48 (5-CH_3), 7.3-7.7 m (Ph), 8.52 (NH), 4.10 (NH_2)
3b	10	50	184-186 (EtOH)	$C_{15}H_{16}N_4O_2$	63.36 62.83	5.67 5.76	19.71 19.47	2220	1645	3440 3490	3.73(N-CH_3), 2.42 (5-CH_3), 3.98 (OCH_3), 6.9-7.8 m (C_6H_4), 8.42 (NH), 4.09 (NH_2)
3c	12	45	193-194 (EtOH)	$C_{15}H_{16}N_4O_2$	63.36 63.61	5.67 5.68	19.71 19.18	2210	1672	3430 3480	3.67 (N-CH_3), 4.53 (CH_2), 2.51 (5-CH_3), 6.9-7.2 m (Ph), 8.14 (NH), 4.69 (NH_2)

Table 3

Cyclization of Hydrazides of Pyrazolcarboxylic Acids with Potassium Hydroxide and Copper(I) Chloride

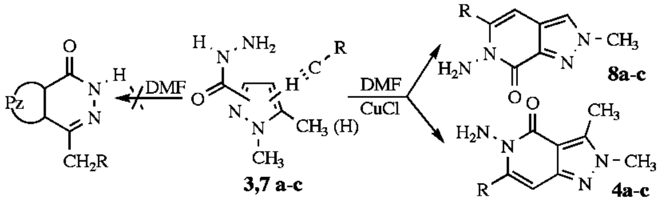
Comp.	Time, hours	Yield, % KOH	Mp °C EtOH	Time, hours	Yield, % CuCl	Mp °C EtOH	Formula	Found Calculated % C	H	N	IR ν, cm^{-1}	^{1}H NMR (deuteriochloroform): δ
8a	5	99	188-189	1.5	50	189-190	$C_{13}H_{12}N_4O$	64.98 64.63	5.03 5.01	23.30 22.98	1661 (C=O) 3400 (NH_2)	4.22 (N-CH_3), 7.71(7-H), 4.96 (NH_2), 6.42 (6-H), 6.9-7.4 m (Ph)
8b	2.5	90	185-187	1	75	185-186	$C_{14}H_{14}N_4O_2$	62.21 62.80	5.22 5.44	20.73 20.80	1656 (C=O) 3410 (NH_2)	3.81 (N-CH_3), 4.11 (OCH_3), 6.10 (6-H), 7.63 (7-H), 4.89 (NH_2), 6.9 (2H) and 7.3 (2H) (AA'BB', J_{ortho} = 9 Hz)
8c	3.5	68	206-207	1	45	205-206	$C_{14}H_{14}N_4O_2$	*			1674 (C=O) 3445 (NH_2)	4.14 (N-CH_3), 5.04 (CH_2), 6.56 (6-H), 7.62 (7-H), 5.12 (NH_2), 6.9-7.3 m (Ph)
4a	7	90	208-209	6	60	209-210	$C_{14}H_{14}N_4O$	66.12 66.01	5.55 5.29	22.03 21.92	1677 (C=O) 3460 (NH_2)	2.75 (7-CH_3), 4.03 (N-CH_3), 7.4-7.8 m (Ph), 6,11 (3-H), 4.22 (NH_2)
4b	10	80	240-241	8	55	238-239	$C_{15}H_{16}N_4O_2$	63.36 63.52	5.67 5.76	19.71 20.25	1669 (C=O) 3436 (NH_2)	3.81 (N-CH_3), 3.87 (OCH_3), 2.58 (7-CH_3) 6.6 (2H) and 7.0 (2H) (AA'BB', J_{ortho} = 9 Hz), 6.10 (3-H), 4.85 (NH_2)
4c	10	50	190-191	2	20	191-192	$C_{15}H_{16}N_4O_2$	63.36 63.25	5.67 5.53	19.71 19.69	1675 (C=O) 3440 (NH_2)	3.97 (N-CH_3), 2.61 (7-CH_3), 5.10 (CH_2), 7.0-7.4 m (Ph), 6.23 (4-H), 4.98 (NH_2)

* MS (70 eV) m/z: 270 [M^+] (3.33), 147.9 (12.73), 149.9 (18,80), 176.9 (100.00). $C_{14}H_{14}N_4O_2$ Mr: found m/z 270.11161; calculated 270.11167.

hours for **3a-c** and 1-3 hours for **7a-c**) in 45-50% yields for **3a-c** and 50-80% for **7a-c** (Table 2).

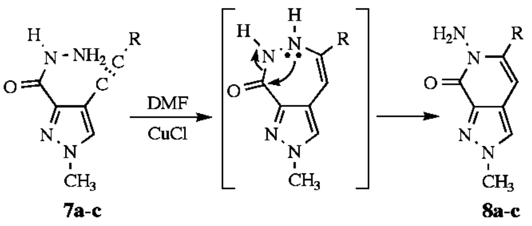
We found unexpected results when exploring the cyclization of hydrazides (**3a-c**) and (**7a-c**) in the presence of copper(I) chloride in boiling dimethylformamide. Both types of hydrazides were transformed into the same *N*-aminolactams **4a-c** and **8a-c** (Scheme 5), already obtained by action of potassium hydroxide in ethanol.

Scheme 5



In basic medium, the most acidic N-H (that of the amido group) would be deprotonated to yield a N$^-$ anion, which in turn would attack the β-carbon of the triple bond. On the other hand, it is difficult to assume that the final product in the case of copper chloride is the result of a direct attack on the triple bond by the nitrogen amide atom. Obviously, in neutral conditions, this nitrogen atom is much less nucleophilic than the terminal amino group. Therefore, we propose that pyrazolopyridones **4** and **8** are formed by isomerization of the primary product of addition of the terminal amine group to the triple bond (Scheme 6). Previously we have described the isomerization of a pyrazolodiazepine (7-membered ring) with ring-contraction into an *N*-aminodiazinone (6-membered ring). Reciprocally, we have found that *N*-aminolactams (isoindolinones) are transformed into diazinones by heating in the presence of copper chloride (in the literature there are data about ring contraction under the action of hydrochloric acid [7]).

Scheme 6



We also investigated other catalysts like copper(I) phenylacetylide, bis-(triphenylphosphine)palladium(II) dichloride and nickel(II) bromide trihydrate (at 80 °C). In all cases, the product of heterocyclization of **7a** was the same *N*-aminolactam (**8a**).

The direction of heterocyclization of **3a-c** and **7a**-**c** in the presence of salts of transition metals is different than that of the hydrazide of 4-phenylethynyl-1-methylpyrazole-5-carboxylic acid (formation of pyridazinones, Scheme 1, class 3 and not of *N*-amino pyridinones, Scheme 2, class **a** [7]). This difference could be related to interrupted conjugation of the groups in the 3 and 4 positions of the pyrazole ring compared with positions 4 and 5 (more double bond character) leading to another transition state.

Coming back to Scheme 1, it should be noted that in benzene derivatives, fused (6,5), (6,6) and (6,7) systems are formed thus covering all possibilities, but in the pyrazole series only (5,6)- and (5,7)-systems have been obtained [7]. (5,5)-Fused systems formed by two 5-membered rings were not formed from these substrates in the reported working conditions. This is correlated with our conclusions in earlier work that, due to ring strain, (5,5)-systems are much more difficult than (5,6) ones [7,10].

Of the four possible cases depicted in Scheme 2, three are now known differences showing between case **a** in one hand and cases **c** and **d** in the other as well as between pyrazole and benzene.

The compounds were identified according to the data reported in Tables 1-3. More precisely, the identity of final compounds, **4** and **8**, was established as follows. Of the four possible structures of Scheme 1, the ways **3** and **4** can be excluded because, both in ir and nmr, is by the observation of an amino group. Therefore, the compounds are *N*-aminolactams (ways **1** and **2** in Scheme 1). To decide if they are five- (way **1**) or six-membered rings (way **2**), we have used the absence of coupling constants in the CH_2 groups in compounds **4c** and **8c**. The fact that there is not an adjacent proton excluded the five membered ring, leaving only the six-membered pyridinones (way **2**). The structure of the remaining compounds, **4a**, **4b**, **8a** and **8b**, are similar and were assigned based on analysis of their ir spectra (see [7] for a related problem).

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker AM-300 spectrometer. IR spectra were recorded on a Bruker IFS 66 spectrometer (potassium bromide). Mass spectra were recorded on a Finnigan SSQ-710 instrument (direct inlet, EI, 70 eV, ionization chamber temperature 220-270 °C). Column chromatography was carried out on KSK silica gel (60-200 µm). Melting points were determined with a Kofler apparatus.

Preparation of Methyl Esters of Ethynylpyrazolecarboxylic Acids (**2a**-**c**, **6a**-**c**).

Compounds **1** or **5** (0.01 mole) and 0.01 mol of RC≡CCu [copper(I) acetylides] in 40 ml pyridine were heated under argon atmosphere (TLC control: Silufol®). The reaction mixture was cooled and poured into chloroform and was washed with aqueous ammonium hydroxide. Chloroform solution was dried over sodium sulfate and was filtered through silica gel (height/diameter of the column: 2.5 x 4 cm), the solvent was eliminated under reduced pressure. The products were recrystallized. The reaction time and the constants of compounds are given in Table 1.

Preparation of Hydrazides of Pyrazolecarboxylic Acides (**3a**-**c**, **7a**-**c**).

Methyl esters of ethynylpyrazolecarboxylic acids (**2a**-**c**, **6a**-**c**) (0.01 mole), 5 ml of 80% hydrazine hydrate in 30 ml of butanol were heated at reflux, cooled and the precipitate was collected by filtration, products were recrystallized from ethanol. The reaction time and the constants of compounds are given in Table 2.

Cyclization of Hydrazides of Pyrazolecarboxylic Acids with Potassium Hydroxide (**4a**-**c**, **8a**-**c**).

Hydrazides of pyrazolecarboxylic acids (**3a**-**c**, **7a**-**c**) (0.01 mole) and 2.5 g of potassium hydroxide were heated in 30 ml of ethanol (TLC control). The solvent was distilled under reduced pressure, the precipitate was dissolved in benzene and filtered through alumina (2.5 x 2 cm), then the benzene was distilled under reduced pressure. The products were recrystallized from ethanol. The reaction times and constants of the compounds are given in Table 3.

Cyclization of Hydrazides of Pyrazolecarboxylic Acids with Copper(I) Chloride (**4a**-**c**, **8a**-**c**).

Hydrazides (**3a**-**c**, **7a**-**c**) (0.01 mole), 0.6 g of copper(I) chloride in 25 ml of dimethylformamide were heated under argon atmosphere. The reaction mixture was cooled and poured into chloroformand was washed with aqueous ammonium hydroxide. The chloroform solution was dried over sodium sulfate and was filtered through alumina (2.5 x 2 cm), the solvent was evaporated under reduced pressure. The products were recrystallized from ethanol. The time of reactions and constants of compounds are given in Table 3.

Cyclization of Hydrazide of Pyrazolecarboxylic Acid (**4c**) with Copper(I) Phenylacetylide.

Hydrazide **3c** (0.001 mole), 0.1 g of copper(I) phenylacetylide (CuC≡CPh) in 5 ml of dimethylformamide were heated under argon atmosphere for 30 minutes. The reaction mixture was cooled and poured into chloroform and was washed with aqueous ammonium hydroxide. Chloroform solution was dried over sodium sulfate and was filtered through alumina (2.5 x 2 cm), and the solvent evaporated. The product was recrystallized from ethanol; yield 0.1 g (35%), mp 205-206 °C.

Cyclization of Hydrazide of Pyrazolecarboxylic Acid (**4c**) with Bis(triphenylphosphine)-palladium(II) Dichloride.

Hydrazide **3c** (0.0009 moles), 0.1 g of bis(triphenylphosphine)palladium(II) dichloride in 5 ml of dimethylformamide were heated under argon atmosphere for 2 hours. The solvent was distilled off under reduced pressure, the precipitated was dissolved in benzene and filtered through alumina (2.5 x 2 cm), the benzene was evaporated. The product was recrystallized from ethanol: yield 0.12 g (48%), mp 205-206 °C.

Cyclization of Hydrazide of Pyrazolecarboxylic Acid (**4c**) with Nickel(II) Bromide Trihydrate.

Hydrazide **3c** (0.0005 moles), 0.06 g of nickel(II) bromide trihydrate in 8 ml of dimethylformamide at 80 °C and under argon atmosphere were refluxed 1 hour. The reaction mixture was cooled and poured into chloroform and was washed with aqueous ammonium hydroxide. Chloroform solution was dried over sodium sulfate and was filtered through alumina (2.5 x 2 cm), then the solvent was evaporated. The product was recrystallized from ethanol; yield 0.05 g (40%), mp 205-206 °C.

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