A New and Convenient Synthesis of 1,2-Diamino-3-hetarylpyrrole Derivatives

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A number of 1-acylamino-2-amino-3-hetaryl-4-oxo-2-pyrrolines **13**–**50** were prepared by treatment of 4-chloro-2-hetaryl-3-oxobutanenitriles **11a**–**h** with substituted benzoic and 2-furanoic acid hydrazides in DMF at 110–120 °C. When the same reagents were coupled in the presence of triethylamine, a definite dependence of the course of the reaction on the nature of the chloronitriles **11a**–**h** was observed. The steric arrangement of the heterocyclic nitrogen atom in chloronitriles **11** seemed to have a critical influence on the nature of the products obtained. Thus, compounds **11d**–**h** with sterically hindered nitrogen atoms gave the pyrrolines **25**–**50** mentioned above, while unhindered derivatives **11a**–**c** afforded products of intramolecular alkylation, namely the 3-cyano-2-oxo-1,2-dihydropyrrolo[1,2-*a*]benzazoles **51**–**53**. An X-ray diffraction study of 2-amino-3-(2-benzothiazolyl)-1-(*p*-nitrobenzoylamino)-4-oxo-2-pyrroline (**24**) was carried out to confirm the structures of compounds **13**–**50** unambiguously. An attempt to extend this reaction to *p*-tolylsulfonylhydrazine resulted in the simple alkylation products **12a**, **12c**, and **12e**, without subsequent ring closure.

Introduction

Over the last 15 years, the chemistry of amino derivatives of pyrrole has attained increasing importance for the following reasons. On the one hand, certain aminopyrrole derivatives have been found to show interesting biological properties[1,2] or have been used as precursors[3] for known drugs. On the other hand, however, aminopyrroles are not readily available through general pyrrole ring-formation methods.[4] To continue our investigations directed towards the synthesis of 2-amino-3-hetarylpyrroles[5,6] and related compounds,[7] we were interested in obtaining corresponding 1,2-diamino derivatives.

Some years ago, O. Attanasi[8] and co-workers developed a simple procedure for preparation of 1,2-diaminopyrroles **4** by addition of active methylenenitriles **1** to the conjugated azoalkenes **2**, with or without isolation of the intermediate hydrazones **3** (Scheme 1). In particular, hetarylacetonitriles **1** (X = 2-benzimidazolyl and 2-benzothiazolyl) were also used in this reaction,[8c] resulting in 1,2-diamino-3-hetarylpyrrole derivatives **4**. Similar pyrroles **8** had been obtained earlier[9] by a two-step procedure based on cycloaddition reactions between nitriles **6** and diazo ketones **7**. However, both methods have some shortcomings connected with side processes. In the first case, this is the formation of a bis(adduct) through the interaction of nitrile **1** with azoalkene **2** in a 1:2 molar ratio[8a,8b] and in the second case it is an alternative pyridazine ring closure.[9] In view of this we turned our efforts to the elaboration of a simple and convenient synthesis of the title derivatives based on another approach. A well-known amination[10] of 4-halobutanenitrile derivatives was chosen as the method for aminopyrrole ring formation, because the required 2-hetaryl-substituted 4-chlorobutanenitriles **11** had been shown to be readily available by direct chloroacetylation[5b−5e,11] of hetarylacetonitriles **9** (Scheme 2). For preparation of 1,2-diaminopyrroles, hydrazine derivatives were to be used instead of amines, although formation of pyridazine derivatives could not be excluded a priori. This paper reports results obtained from research into the interaction between compounds **11** and carboxylic and sulfonic acid hydrazides.

Results and Discussion

Two kinds of conditions, nonbasic (i) and basic (ii), were employed to carry out the reaction between 4-chloro-2-hetaryl-3-oxobutanenitriles **11a**−**h** and substituted benzoic and 2-furanoic acid hydrazides **12a**−**g** (Scheme 2). When 2-(4-aryl)thiazolyl derivatives **11d**−**h** were used as starting materials, 1-acylamino-2-amino-3-hetaryl-4-oxo-2-pyrrolines **25**−**50** were isolated under both basic and nonbasic conditions in 60−80% yields. These compounds were assumed to be formed by alkylation of the primary amino group of hydrazide **12** followed by intramolecular addition of the obtained NH group to the nitrile triple bond. At the

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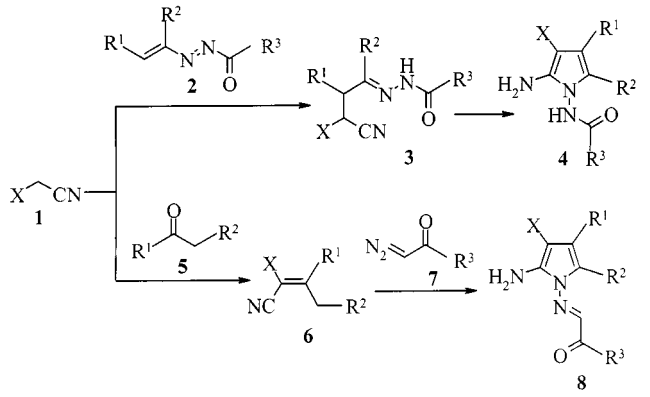
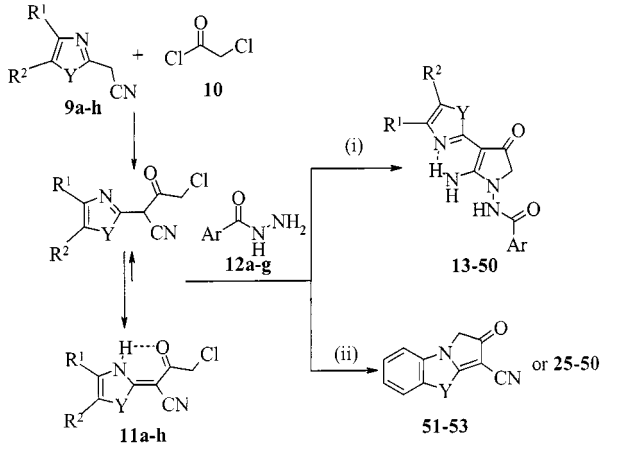


Scheme 1. Known methods for the preparation of the title derivatives; X is an electron-withdrawing group



Scheme 2. Reagents and conditions: (i) DMF, 110−120 °C; (ii) dioxane, 1 equiv. Et_3N; for R^1, R^2 and Y see Table 1

same time, the benzothiazolyl and benzimidazolyl derivatives **11a−c** exclusively gave the corresponding pyrroles **13−24** under nonbasic conditions. In the presence of triethylamine, they underwent an intramolecular alkylation, resulting in the formation of the previously described[5b] pyrrolobenzazoles **51−53**. Experimental data for the prepared compounds are listed in Table 1.

Since the basicities of benzothiazolyl and thiazolyl derivatives **11** are almost equal, the different behavior of compounds **11a−c** and **11d−h** under basic conditions can be explained only in terms of steric factors. Thus, in the case of the thiazolyl derivatives **11d−h**, the substituent R^1 is believed to shield a heterocyclic nitrogen atom, producing hindrance for intramolecular alkylation. Since such an effect is absent in compounds **11a−c**, they are smoothly converted into derivatives **51−53** by the action of any base. This is in accordance with our previous findings on this matter. Thus, the benzo derivatives **11a−c** were shown to be readily and almost quantitatively transformed into pyrrolobenzazoles **51−53** under conditions of type (ii),[5a,5b] while compounds **11d** and **11e** were found to be much less active toward similar transformations and gave the corresponding products only in low yields under the same conditions.[11c]

The structures of pyrroles **13−50** were initially deduced from their ^1H NMR and IR spectra. The ^1H NMR spectra of compounds **13−50** recorded in [D_6]DMSO showed signals from the heterocyclic moiety and the aryl group at their expected δ values, as well as a two-proton singlet (methylene) at δ = 3.9−4.2 and D_2O-exchangeable signals (amide NH and NH_2 groups) at δ = 10.7−11.2 and 8.5−9.2, respectively. Full ^1H NMR spectroscopic data for compounds **13−50** are available as electronic supporting information; see footnote on the first page of this article. The latter set of signals sometimes appeared as two broadened one-proton singlets, because of an intramolecular hydrogen bond, as illustrated in Scheme 2. Similar hydrogen bonds were observed for related systems.[5a,5d,5e,6] Several strong and medium absorption bands corresponding to different NH vibrations were present at 3100−3340 cm^{-1} in the IR spectra of derivatives **13−50**. A strong band at 1640−1650 cm^{-1} was assigned to the amide carbonyl absorption. The absence of CN absorption clearly indicates CN participation in ring closure. Thus, according to the spectroscopic data, compounds **13−50** exist as amino−oxo tautomers, without any detectable quantity of other possible tautomeric forms, at least in [D_6]DMSO solution.

A pyridazine structure such as **54** (Figure 1) may be taken into consideration as an alternative for pyrroles **13−50**. However, there are some disagreements between it and the observed spectroscopic data. If the structure **54** were true, then the signal at δ = 10.7−11.2 has to be assigned to the 2-H of pyridazine. This, however, is too large a value for such a type of protons. Moreover, the signal of the methylene group in structure **54** might be split due to spin-spin coupling with NH. However, splitting was never observed in all the compounds prepared.

Nevertheless, in order to confirm the structure of pyrroles **13−50** unambiguously and to remove any doubt, an X-ray diffraction study of 2-amino-3-(2-benzothiazolyl)-1-(*p*-nitrobenzoylamino)-4-oxo-2-pyrroline (**24**) was carried out (Figure 2). According to the crystallographic data, the benzothiazole and pyrrole rings of **24**, as well as the oxo group O(4) and the amino group N(4) are approximately coplanar. The phenyl ring protrudes from this plane at an angle of about 73°. The C(7)=O(3) carbonyl group deviates from the phenyl ring plane [dihedral angle C(6)−C(5)−C(7)−O(3) is 18.6°], due to repulsion between the hydrogen atoms at C(4) and N(2) (the distance is 2.103 Å, the sum of the van der Waals radii[12] is 2.32 Å). The pyrrole ring adopts an envelope conformation, with the N(3) atom bent out from the plane of C(8), C(9), C(10), C(11) at the value of 0.16 Å.

It is interesting to note that the bonds C(10)−O(4) and C(8)−C(11) are significantly longer (1.244 Å and 1.414 Å, respectively) than their average values (1.210 Å and 1.316 Å, respectively[13]), while the bonds N(4)−C(8) and C(10)−C(11) are shorter (1.324 Å and 1.429 Å while the mean values[13] are 1.336 Å and 1.445 Å). These distortions

Table 1. Experimental data for compounds **13**−**53**

Starting materials **11**	R^1	R^2	Y	**12**	Ar	Method	Product	Yield%[a]
11a	benzo		NH	**12a**	4-$CH_3C_6H_4$	(i)	**13**	63
11a	benzo		NH	**12b**	3,4-$(MeO)_2C_6H_3$	(i)	**14**	74
11a	benzo		NH	**12c**	3-$MeOC_6H_4$	(i)	**15**	71
11a	benzo		NH	**12d**	2-$O_2NC_6H_4$	(i)	**16**	86
11a	benzo		NH	**12e**	2-furyl	(i)	**17**	74
11a	benzo		NH	**12g**	4-BrC_6H_4	(i)	**18**	81
11b	benzo		NCH_3	**12c**	3-$MeOC_6H_4$	(i)	**19**	69
11c	benzo		S	**12b**	3,4-$(MeO)_2C_6H_3$	(i)	**20**	79
11c	benzo		S	**12c**	3-$MeOC_6H_4$	(i)	**21**	77
11c	benzo		S	**12d**	2-$O_2NC_6H_4$	(i)	**22**	78
11c	benzo		S	**12e**	2-furyl	(i)	**23**	72
11c	benzo		S	**12f**	4-$O_2NC_6H_4$	(i)	**24**	80
11d	4-ClC_6H_4	H	S	**12b**	3,4-$(MeO)_2C_6H_3$	(i/ii)[b]	**25**	76
11d	4-ClC_6H_4	H	S	**12c**	3-$MeOC_6H_4$	(i/ii)[b]	**26**	71
11d	4-ClC_6H_4	H	S	**12d**	2-$O_2NC_6H_4$	(i/ii)[b]	**27**	72
11d	4-ClC_6H_4	H	S	**12f**	4-$O_2NC_6H_4$	(i/ii)[b]	**28**	78
11e	4-BrC_6H_4	H	S	**12a**	4-$CH_3C_6H_4$	(i/ii)[b]	**29**	68
11e	4-BrC_6H_4	H	S	**12b**	3,4-$(MeO)_2C_6H_3$	(i/ii)[b]	**30**	73
11e	4-BrC_6H_4	H	S	**12c**	3-$MeOC_6H_4$	(i/ii)[b]	**31**	70
11e	4-BrC_6H_4	H	S	**12d**	2-$O_2NC_6H_4$	(i/ii)[b]	**32**	70
11e	4-BrC_6H_4	H	S	**12e**	2-furyl	(i/ii)[b]	**33**	78
11e	4-BrC_6H_4	H	S	**12f**	4-$O_2NC_6H_4$	(i/ii)[b]	**34**	76
11e	4-BrC_6H_4	H	S	**12g**	4-BrC_6H_4	(i/ii)[b]	**35**	65
11f	3-$O_2NC_6H_4$	H	S	**12a**	4-$CH_3C_6H_4$	(i/ii)[b]	**36**	75
11f	3-$O_2NC_6H_4$	H	S	**12b**	3,4-$(MeO)_2C_6H_3$	(i/ii)[b]	**37**	69
11f	3-$O_2NC_6H_4$	H	S	**12c**	3-$MeOC_6H_4$	(i/ii)[b]	**38**	70
11f	3-$O_2NC_6H_4$	H	S	**12d**	2-$O_2NC_6H_4$	(i/ii)[b]	**39**	71
11f	3-$O_2NC_6H_4$	H	S	**12e**	2-furyl	(i/ii)[b]	**40**	71
11f	3-$O_2NC_6H_4$	H	S	**12f**	4-$O_2NC_6H_4$	(i/ii)[b]	**41**	76
11f	3-$O_2NC_6H_4$	H	S	**12g**	4-BrC_6H_4	(i/ii)[b]	**42**	66
11g	4-$CH_3C_6H_4$	H	S	**12a**	4-$CH_3C_6H_4$	(i/ii)[b]	**43**	72
11g	4-$CH_3C_6H_4$	H	S	**12b**	3,4-$(MeO)_2C_6H_3$	(i/ii)[b]	**44**	79
11g	4-$CH_3C_6H_4$	H	S	**12c**	3-$MeOC_6H_4$	(i/ii)[b]	**45**	80
11g	4-$CH_3C_6H_4$	H	S	**12d**	2-$O_2NC_6H_4$	(i/ii)[b]	**46**	80
11g	4-$CH_3C_6H_4$	H	S	**12e**	2-furyl	(i/ii)[b]	**47**	74
11g	4-$CH_3C_6H_4$	H	S	**12f**	4-$O_2NC_6H_4$	(i/ii)[b]	**48**	68
11g	4-$CH_3C_6H_4$	H	S	**12g**	4-BrC_6H_4	(i/ii)[b]	**49**	73
11h	1-adamantyl	H	S	**12b**	3,4-$(MeO)_2C_6H_3$	(i/ii)[b]	**50**	77
11a	benzo		NH	[c]	[c]	(ii)	**51**	86
11b	benzo		NCH_3	[c]	[c]	(ii)	**52**	90
11c	benzo		S	[c]	[c]	(ii)	**53**	84

[a] The yield of pure isolated product. [b] The yield is stated for method (i). Method (ii) gives similar results with no more than 5% differences. [c] Any of **12a**−**g**.

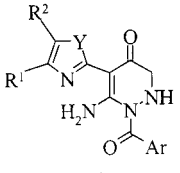


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Figure 1. Possible alternative structure for pyzzoles **13**−**50**

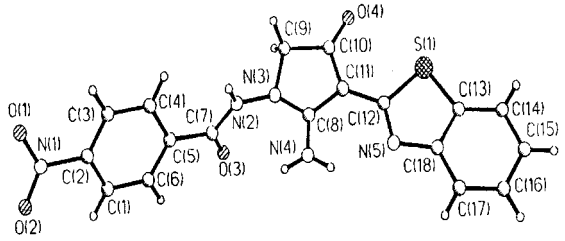
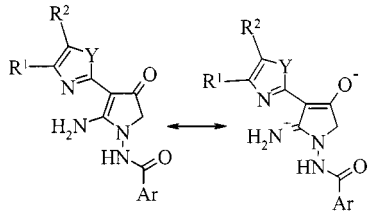


Figure 2. X-ray molecular structure of compound **24** with the atom numbering system used in the crystallographic analysis

indicate a considerable contribution from the bipolar canonic structure established in Scheme 3.

That is in agreement with certain experimental observations. Thus, all attempts to close a triazole ring by intramolecular condensation of the amino group and the amide carbonyl group failed. Only starting material was recovered after treatment of compound **24** with polyphosphoric acid, $POCl_3$, or PCl_5, either under gentle heating or at reflux. Prolonged reflux resulted in unidentified tars being obtained. This failure is believed to be due to the low nucleophilicity of the amino group, as explained by the canonic structure discussed above. The same reason probably lays

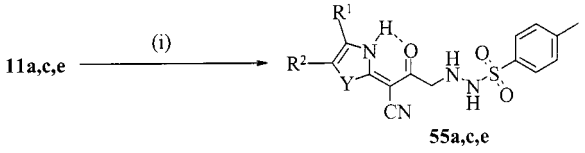


Scheme 3

behind unsuccessful attempts to acylate compounds **13**−**50** under standard conditions (benzoyl chloride in pyridine or excess of Ac_2O). A similar resonance has been noted as typical for simple enamino ketones.[14]

To resume, the chloronitriles **11a**−**h** had been shown to be suitable precursors for the preparation of 1,2-diamino-3-hetarylpyrrole derivatives similar to those (**4**) obtained by O. Attanasi[8] and co-workers, but with further substitution at positions 4 and 5 of the pyrrole ring. Unlike Attanasi's[8] and related[9] methods, this approach has no shortcomings associated with side processes, at least in modification (i). Moreover, it allows widely varying substituents at the first and third positions. Finally, the starting materials used are readily available and stable compounds and can be kept for any time required. This is a considerable advantage of this procedure, since the described methods[8,9] use certain labile and difficult to store azoalkenes **2**[3,15] or diazo ketones **7**.[9]

Further investigations were directed to extending the scope of the method for preparation of the corresponding 1-arylsulfonylamino derivatives. However, treatment of chloronitriles **11a**, **11c**, and **11e** with *p*-tolylsulfonylhydrazine resulted only in the simple alkylation products **55a**, **55c**, and **55e** (Scheme 4), without subsequent ring closure. In contrast, Attanasi's method allowed 1-arylsulfonylamino derivatives of pyrrole to be obtained starting from arylsulfonylazoalkenes.[16] The structures of compounds **55a**, **55c**, and **55e** were assigned on the basis of their IR and ^{1}H NMR spectra. In particular, the IR spectra showed strong nitrile absorptions at about 2180 cm^{-1}, while the absence of amino group signals and the presence of signals from the heterocyclic moiety and the *p*-tolyl residue were observed in the ^{1}H NMR spectra. Like the starting chloronitriles **11a**, **11c**, and **11e**, compounds **55** exist as NH tautomers with intramolecular hydrogen bonds (the NH···O signals were at δ = 12.9−13.0).



Scheme 4. Reagents and conditions: (i) $TsNHNH_2$, DMF, 110−120 °C

In conclusion, this investigation has resulted in the elaboration of a new and convenient method for preparation of 1-acylamino-2-amino-3-hetarylpyrrole derivatives **13**−**50**, starting from readily available materials. Unfortunately, it was found to be inapplicable for the synthesis of 1-arylsulfonylamino analogues. Nevertheless, it makes a good alternative to the previous reported procedures.[8,9]

Experimental Section

General: Chloronitriles **11a**−**e**,**h** were prepared as previously reported.[5e,5d,11a,11c,11d] Hydrazides **12a**−**g** are commercially available materials. All reactions were monitored by TLC on Silufol UV-254 plates with chloroform/methanol (9:1) as eluent. All IR spectra were obtained with KBr tablets and were recorded with a Pye Unicam SP 3−300 apparatus. ^{1}H NMR spectra were recorded with a Bruker WP 100 SY (100 MHz) spectrometer in $(CD_3)_2SO$ solution. Chemical shifts (δ) are reported in ppm downfield from internal $SiMe_4$; *J* values are in Hz. The abbreviations used are as follows: s singlet, d doublet, t triplet, dd doublet of doublets, br. broad. All m.p. values were determined in capillary tubes in a Thiele apparatus and are uncorrected. The purity of all compounds prepared was monitored by TLC and ^{1}H NMR.

4-(3-Nitrophenyl)-2-thiazolylacetonitrile (9f): 3-Nitrophenacyl bromide (73 g, 0.3 mol) was added quickly in 3−4 portions to a warm (40−50 °C) solution of cyanothioacetamide (30 g, 0.3 mol) in ethanol (400 mL). The temperature was allowed to increase to boiling and the mixture self-refluxed for several minutes. During this time, all the 3-nitrophenacyl bromide dissolved and crystals of **9f**·HBr began to separate from the warm solution. After cooling, the crystals were filtered off and then suspended in conc. aq. ammonia for 1 h. After filtration, crude **9f** was obtained. It was recrystallized from *i*PrOH to give 60 g (82%) of pure **9f**. M.p. 136 °C. ^{1}H NMR: δ = 4.76 (s, 2 H, CH_2), 7.76 (t, 1 H, *J* = 7.5 Hz, 5-H_{R1}), 8.22 (dd, 1 H, *J* = 7.5, *J* = 1.9 Hz, 6-H_{R1}), 8.40 (dd, 1 H, *J* = 7.5 Hz, *J* = 1.9 Hz, 4-H_{R1}), 8.45 (s, 1 H, R^2), 8.75 (t, 1 H, *J* = 1.9 Hz, 2-H_{R1}). $C_{11}H_7N_3O_2S$ (245.26): calcd. C 53.87, H 2.88, N 17.13, S 13.07; found C 53.72, H 2.90, N 17.17, S 12.98.

4-Chloro-2-[4-(3-nitrophenyl)-2,3-dihydro-1,3-thiazol-2-ylidene]-3-oxobutanenitrile (11f): Chloroacetyl chloride (16 mL, 0.2 mol) was added portionwise with caution to a solution of nitrile **9f** (49 g, 0.2 mol) and pyridine (17 mL) in dioxane (70 mL). The resulted mixture was heated on a water bath for 1 h and was then concentrated to dryness in vacuo. The residue was treated with water and filtered. The crude product was recrystallized from acetonitrile to give **11f** (36 g, 56%). M.p. 185 °C. ^{1}H NMR: δ = 4.50 (s, 2 H, CH_2), 7.76 (t, 1 H, *J* = 7.8 Hz, 5-H_{R1}), 7.85 (s, 1 H, R^2), 8.26 (m, 2 H, 4,6-H_{R1}), 8.67 (t, 1 H, *J* = 2.0, 2-H_{R1}), 12.88 (1 H, br s, NH···O). $C_{13}H_8ClN_3O_3S$ (321.74): calcd. C 48.53, H 2.51, Cl 11.02, N 13.06, S 9.97; found C 48.47, H 2.62, Cl 11.11, N 12.99, S 9.98

4-Chloro-2-[4-(4-methylphenyl)-2,3-dihydro-1,3-thiazol-2-ylidene]-3-oxobutanenitrile (11g): Chloroacetyl chloride (16 mL, 0.2 mol) was added portionwise with caution to a solution of nitrile **9g**[17] (42.8 g, 0.2 mol) and pyridine (17 mL) in dioxane (70 mL). Yellow crystals separated after a few minutes. The mixture was heated on a water bath for 40 min. The precipitate was filtered off and thoroughly washed with water. The product obtained (51 g, 88%) was used without further purification. The analytical sample of **11g** was additionally purified by recrystallization from dioxane. M.p. 230 °C. ^{1}H NMR: δ = 2.36 (s, 3 H, CH_3), 4.47 (s, 2 H, CH_2), 7.30 (d, 2 H, *J* = 9.0 Hz, R^1), 7.46 (s, 1 H, R^2), 7.66 (d, 2 H, *J* = 9.0 Hz, R^1), 12.88 (br s, 1 H, NH···O). $C_{14}H_{11}ClN_2OS$ (290.77): calcd. C

57.83, H 3.81, Cl 12.19, N 9.63, S 11.03; found C 57.89, H 3.77, Cl 12.22, N 9.71, S 10.97.

Preparation of 1-Acylamino-2-amino-3-hetaryl-4-oxo-2-pyrrolines 13−50. − Method (i): A solution of chloronitrile **11a−h** (2 mmol) and hydrazide **12a−g** (2 mmol) in DMF (3 mL) was heated at 110−120° for 1−2 h until complete disappearance of compounds **11a−h** from the reaction mixture (TLC). After cooling, the formed precipitate was filtered, washed with water, and dried at 100 °C for 3−4 h. In most cases the substances obtained were analytically pure. If necessary they were purified by recrystallization from DMF. − **Method (ii):** Hydrazide **12a−g** (2 mmol) was added to a solution of chloronitrile (2 mmol) and triethylamine (0.35 mL, 2.5 mmol) in dioxane (5 mL). The mixture was heated under reflux for 1−2 h until complete disappearance of compounds **11a−h** (TLC). After cooling, the mixture was elaborated as in method (i). If chloronitriles **11d−h** were used as starting materials, pyrroles **25−50** were isolated. The use of chloronitriles **11a−c** resulted in isolation of pyrrolobenzazoles **51−53** independently of the hydrazide used. For yields and analytical data see Tables 1 and 2.

2-Hetaryl-3-oxo-4-[2-(*p*-tolylsulfonyl)hydrazino]butanenitriles 55a, 55c, and 55e: A solution of chloronitrile **11a**, **11c**, or **11e** (2 mmol) and *p*-tolylsulfonylhydrazine (0.38 g, 2 mmol) in DMF (3 mL) was heated at 110−120° for 1−2 h until the complete disappearance of compounds **11a**, **11c**, or **11e** from the reaction mixture (TLC). After cooling, the mixture was elaborated as in method (i) to yield compounds **55a**, **55c**, or **55e**.

2-(2-Benzimidazolyl)-3-oxo-4-[2-(*p*-tolylsulfonyl)hydrazino]butanenitrile (55a): (0.53 g, 70%). M.p. 265 °C (from DMF). ^{1}H NMR: δ = 2.40 (s, 3 H, CH_3), 4.52 (s, 2 H, CH_2), 6.13 (1 H, br s, CH_2*NH*),

Table 2. Analytical data for compounds **13−53**

Product (empirical formula)[a]	M.p. [°C]	Found (calcd.)[a]			
		C	H	N	S
13 ($C_{19}H_{17}N_5O_2$)	> 300	65.74 (65.70)	5.01 (4.93)	20.19 (20.16)	−
14 ($C_{20}H_{19}N_5O_4$)	> 300	61.00 (61.06)	4.90 (4.87)	17.74 (17.80)	−
15 ($C_{19}H_{17}N_5O_3$)	> 300	62.79 (62.80)	4.69 (4.72)	19.22 (19.27)	−
16 ($C_{18}H_{14}N_6O_4$)	311	57.13 (57.14)	3.74 (3.73)	22.18 (22.21)	−
17 ($C_{16}H_{13}N_5O_3$)	317	59.41 (59.44)	4.01 (4.05)	21.65 (21.66)	−
18 ($C_{18}H_{14}BrN_5O_2$)	> 300	52.39 (52.44)	3.38 (3.42)	17.06 (16.99)	−
19 ($C_{20}H_{19}N_5O_3$)	303	63.71 (63.65)	4.99 (5.07)	18.51 (18.56)	−
20 ($C_{20}H_{18}N_4O_4S$)	> 300	58.47 (58.53)	4.37 (4.42)	13.66 (13.65)	7.90 (7.81)
21 ($C_{19}H_{16}N_4O_3S$)	> 300	60.03 (59.99)	4.20 (4.24)	14.79 (14.73)	8.42 (8.43)
22 ($C_{18}H_{13}N_5O_4S$)	313	54.77 (54.68)	3.30 (3.31)	17.68 (17.71)	811 (8.11)
23 ($C_{16}H_{12}N_4O_3S$)	315	56.44 (56.46)	3.59 (3.55)	16.51 (16.46)	9.48 (9.42)
24 ($C_{18}H_{13}N_5O_4S$)	> 300	54.62 (54.68)	3.27 (3.31)	17.66 (17.71)	8.04 (8.11)
25 ($C_{22}H_{19}ClN_4O_4S$)	> 300	56.15 (56.11)	3.99 (4.07)	11.88 (11.90)	6.88 (6.81)
26 ($C_{21}H_{17}ClN_4O_3S$)	> 300	57.19 (57.21)	3.95 (3.89)	12.64 (12.71)	7.22 (7.27)
27 ($C_{20}H_{14}ClN_5O_4S$)	> 300	52.66 (52.69)	3.11 (3.10)	15.42 (15.36)	6.98 (7.03)
28 ($C_{20}H_{14}ClN_5O_4S$)	> 300	52.72 (52.69)	3.06 (3.10)	15.40 (15.36)	6.99 (7.03)
29 ($C_{21}H_{17}BrN_4O_2S$)	> 300	53.77 (53.74)	3.66(3.65)	12.03 (11.94)	6.88 (6.83)
30 ($C_{22}H_{19}BrN_4O_4S$)	306	51.29 (51.27)	3.68 (3.72)	10.81 (10.87)	6.19 (6.22)
31 ($C_{21}H_{17}BrN_4O_3S$)	> 300	52.04 (51.97)	3.59 (3.53)	11.49 (11.54)	6.54 (6.61)
32 ($C_{20}H_{14}BrN_5O_4S$)	> 300	47.98 (48.01)	2.79 (2.82)	13.92 (14.00)	6.41 (6.41)
33 ($C_{18}H_{13}BrN_4O_3S$)	> 300	48.52 (48.55)	3.00 (2.94)	12.54 (12.58)	7.28 (7.20)
34 ($C_{20}H_{14}BrN_5O_4S$)	> 300	47.94 (48.01)	2.77 (2.82)	14.08 (14.00)	6.44 (6.41)
35 ($C_{20}H_{14}Br_2N_4O_2S$)	294	44.90 (44.97)	2.59 (2.64)	10.56 (10.49)	5.91 (6.00)
36 ($C_{21}H_{17}N_5O_4S$)	> 300	58.01 (57.92)	3.88 (3.93)	16.14 (16.08)	7.33 (7.36)
37 ($C_{22}H_{19}N_5O_6S$)	> 300	54.82 (54.88)	4.03 (3.98)	14.49 (14.55)	6.58 (6.66)
38 ($C_{21}H_{17}N_5O_5S$)	> 300	55.92 (55.87)	3.84 (3.80)	15.47 (15.51)	7.19 (7.10)
39 ($C_{20}H_{14}N_6O_6S$)	> 300	51.48 (51.50)	2.98 (3.03)	17.95 (18.02)	6.81 (6.87)
40 ($C_{18}H_{13}N_5O_5S$)	> 300	52.61 (52.55)	3.24 (3.19)	17.09 (17.02)	7.81 (7.79)
41 ($C_{20}H_{14}N_6O_6S$)	> 300	51.44 (51.50)	2.99 (3.03)	18.11 (18.02)	6.84 (6.87)
42 ($C_{20}H_{14}BrN_5O_4S$)	> 300	47.96 (48.01)	2.74 (2.82)	13.92 (14.00)	6.32 (6.41)
43 ($C_{22}H_{20}N_4O_2S$)	> 300	65.39 (65.33)	5.02 (4.98)	13.91 (13.85)	8.00 (7.93)
44 ($C_{23}H_{22}N_4O_4S$)	> 300	61.39 (61.32)	4.94 (4.92)	12.39 (12.44)	7.11 (7.12)
45 ($C_{22}H_{20}N_4O_3S$)	310	62.81 (62.84)	4.71 (4.79)	13.33 (13.32)	7.59 (7.63)
46 ($C_{21}H_{17}N_5O_4S$)	> 300	58.03 (57.92)	4.00 (3.93)	16.02 (16.08)	7.40 (7.36)
47 ($C_{19}H_{16}N_4O_3S$)	> 300	60.04 (59.99)	4.21 (4.24)	14.71 (14.73)	8.38 (8.43)
48 ($C_{21}H_{17}N_5O_4S$)	317	57.99 (57.92)	4.00 (3.93)	16.00 (16.08)	7.33 (7.36)
49 ($C_{21}H_{17}BrN_4O_2S$)	> 300	53.72 (53.74)	3.66 (3.65)	12.03 (11.94)	6.91 (6.83)
50 ($C_{26}H_{30}N_4O_4S$)	> 300	63.14 (63.14)	6.05 (6.11)	11.39 (11.33)	6.44 (6.48)
51 ($C_{11}H_7N_3O$)	[b]	[b]	[b]	[b]	[b]
52 ($C_{12}H_9N_3O$)	[b]	[b]	[b]	[b]	[b]
53 ($C_{11}H_6N_2OS$)	[b]	[b]	[b]	[b]	[b]

[a] For compounds **18**, **25−35**, **42**, and **49**, analysis for halogen was also carried out and data were in good agreement with those required. [b] The data were in agreement with those reported in ref.[5b] Mixed m.p. samples and IR spectra confirmed the identity of compounds **51−53** with the previously described ones.

7.28 (m, 2 H, R^1R^2), 7.44 (d, 2 H, J = 8.0 Hz, *p*-tolyl), 7.53 (m, 2 H, R^1R^2), 7.81 (d, 2 H, J = 8.0 Hz, *p*-tolyl), 9.10 (s, 1 H, SO_2NH), 12.95 (br s, 2 H, NH). $C_{18}H_{17}N_5O_3S$ (383.43): calcd. C 56.39, H 4.47, N18.26, S 8.36; found C 56.44, H 4.41, N 18.24, S 8.39.

2-(2-Benzothiazolyl)-3-oxo-4-[2-(*p*-tolylsulfonyl)hydrazino]butanenitrile (55c): (0.6 g, 75%). M.p. 268 °C (from DMF). ^{1}H NMR: δ = 2.40 (s, 3 H, CH_3), 4.62 (s, 2 H, CH_2), 6.24 (br s, 1 H, CH_2NH), 7.60−7.30 (m, 4 H, *p*-tolyl and R^1R^2), 7.77 and 7.72 (d, 3 H, J = 9.0 Hz, *p*-tolyl and dd, J = 7.5, J = 1.0 Hz, R^1R^2), 8.00 (dd, 1 H, J = 7.5, J = 1.0 Hz, R^1R^2), 9.12 (s, 1 H, SO_2NH), 13.03 (br s, 1 H, NH···O). $C_{18}H_{16}N_4O_3S_2$ (400.48): calcd. C 53.99, H 4.03, N 13.99, S 16.01; found C 54.06, H 4.09, N 14.03, S 16.08.

2-[4-(*p*-Bromophenyl)thiazol-2-yl]-3-oxo-4-[2-(*p*-tolylsulfonyl)-hydrazino]butanenitrile (55e): (0.96 g, 96%). M.p. 215 °C (from BuOH). ^{1}H NMR: δ = 2.40 (s, 3 H, CH_3), 4.57 (s, 2 H, CH_2), 6.17 (br s, 1 H, CH_2NH), 7.43 (d, 2 H, J = 9.0 Hz, *p*-tolyl), 7.57 (s, 1 H, R^2), 7.70 (m, 6 H, R^1 and *p*-tolyl), 9.10 (s, 1 H, SO_2NH), 11.44 (br s, 1 H, NH···O). $C_{20}H_{17}BrN_4O_3S_2$ (505.42): calcd. C 47.53, H 3.39, Br 15.81, N 11.09, S 12.69; found C 47.49, H 3.44, Br 15.78, N 11.01, S 12.63.

Crystal Structure Determination of Compound 24: Single crystals of **24** were obtained from DMF. Intensity data were collected with a Siemens P3/PC diffractometer using 2θ/θ scan, $2\theta_{max}$ = 50°, Mo-K_α radiation. Crystal data: $C_{18}H_{13}N_5O_4S$, M = 395.40, orthorhombic, a = 13.516(3), b = 7.251(2), c = 36.431(8) Å, V = 3570.4(15) Å^3, T = 293 K, space group *Pbca*, Z = 8, μ(Mo-K_α) = 0.218 mm^{-1}, 2910 reflections measured, all unique, which were used in all calculations. Structure determination and refinement: The structure was solved by direct methods with the SHELX97 program package.[18] The positions of hydrogen atoms were located by Fourier difference synthesis and refined by a riding model with U_{iso} = 1.2 U_{eq} of non-hydrogen atom bonded with hydrogen atom given. The structure was refined by full-matrix, least-squares methods, using anisotropic thermal parameters for all non-hydrogen atoms. The final $wR(F^2)$ value was 0.1424, S = 1.009 (all data).

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