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New Syntheses of 2,4-Diaminopyrroles and Aminopyrrolinones

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Summary. Oxazolin-2-ylidene-malononitriles **3a–d**, obtainable from thioketenaminals and α-halogen-ketones, react with primary and secondary amines to afford 2,4-diamino-pyrroles **5a–h**. Mercaptobenzen as nucleophilic agent gives the 4-amino-2-phenylthio-pyrrole **5j**. Analogously, cyano-(3,5-diphenyl-3*H*-oxazol-2-ylidene)-acetic acid methyl esters were prepared as intermediates for the synthesis of 2-amino-4-oxo-pyrrolines **10a–d**. The isomeric 4-amino-2-oxo-pyrrolines **13a–d** can be obtained from 4-amino-2-methoxy-pyrroles, which serves as proof for the position of substituents. The structures were investigated by ^{1}H and ^{13}C NMR spectroscopy.

Keywords. *Thorpe-Ziegler* cyclization; (Oxazolin-2-yliden)malononitrile; 2,4-Diamino-pyrrole; 2-Amino-4-oxo-pyrrol-3-carbonitrile; 4-Amino-2-oxo-pyrrol-3-carbonitrile.

Neue Synthesen von 2,4-Diaminopyrrolen und Aminopyrrolinonen

Zusammenfassung. Die Oxazolin-2-yliden-malononitrile **3a–d**. die aus Thioketenaminalen und α-Halogenketonen erhalten wurden, reagieren mit primären und sekundären Aminen zu den 2,4-Diaminopyrrolen **5a–h**. Mercaptobenzol als nukleophiles Reagens liefert 4-Amino-2-phenylthio-pyrrol (**5j**). Analog wurden Cyan-(3,5-diphenyl-3*H*-oxazol-2-yliden)-essigsäuremethylester als Zwischenprodukte für die Synthese der 2-Amino-4-oxo-pyrroline **10a–d** hergestellt. Die isomeren 4-Amino-2-oxo-pyrroline **13a–d** können aus den 4-Amino-2-methoxy-pyrrolen **11a**, **b** erhalten werden, was als Nachweis für die Position der Substituenten dient. Die Verbindungen wurden ^{1}H- und ^{13}C NMR-spektroskopisch untersucht.

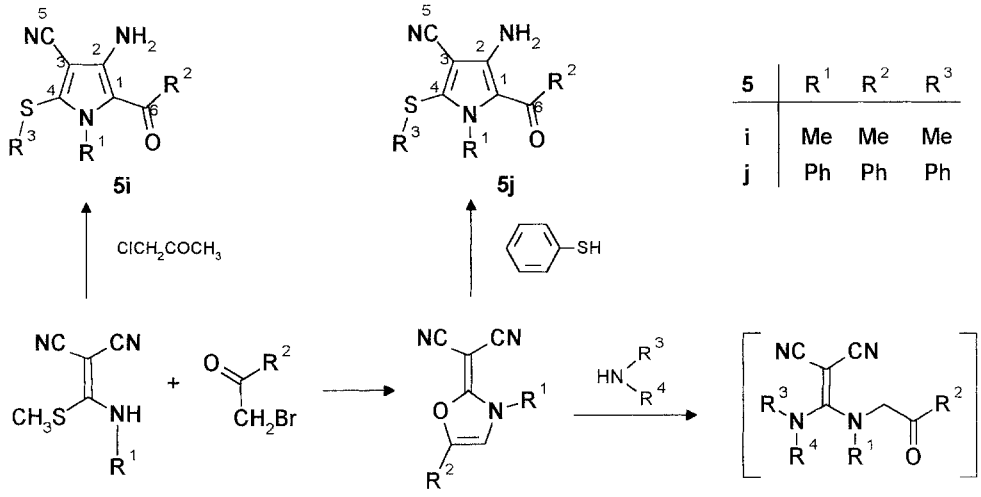
Introduction

Earlier, we have reported on the reaction of thioketene aminals **1**, obtained from malononitrile and isothiocyanates, with α-halogen-ketones to give (oxazolin-2-ylidene)malononitriles **3** which undergo a ring transformation to 2-alkoxy-4-amino-pyrroles upon treatment with alcoholates [1]. Under similar conditions, (oxazol-2-ylidene)cyanamides were employed to afford 2-alkoxy-4-amino- and 2,4-diamino-imidazoles [2].

The present paper deals with the reactions of (oxazolin-2-ylidene)malononitriles (**3**) and cyano-(oxazolin-2-ylidene)-acetic acid esters (**8**) with amines and thioles.

Results and Discussion

We have established that secondary amines react smoothly with (oxazolin-2-ylidene)malononitriles **3**. It can be supposed that the amine attacks the oxazoline to cleave the ring at position 2 leading to a not isolable ketene aminal **4** which thereafter undergoes a *Thorpe-Ziegler* cyclization [1] affording 2,4-diamino-pyrroles **5a–h**. There are many examples describing the synthesis of 3-amino-pyrroles by *Thorpe-Ziegler* cyclization [1, 3–5]. 2,4-Diamino-pyrroles are hitherto unknown. The electron-withdrawing groups at positions 3 and 5 exert a stabilizing effect on the 2,4-diamino-pyrroles **5**.



5	R^1	R^2	R^3
i	Me	Me	Me
j	Ph	Ph	Ph

1	3	R^1	R^2
a	a	Ph	Ph
b	b	Me	Ph
–	c	Ph	Me
–	d [a]	Me	Me

a) 3 not obtainable

5	R^1	R^2	R^3	R^4
a	Ph	Ph	$-(CH_2)_2-O-(CH_2)_2-$	
b	Ph	Ph	$-(CH_2)_5-$	
c	Ph	Ph	Me	Me
d	Ph	Me	$-(CH_2)_2-O-(CH_2)_2-$	
e	Ph	Me	$-(CH_2)_5-$	
f	Me	Ph	$-(CH_2)_5-$	
g [b]	Ph	Ph	H	n-Butyl
h [b]	Ph	Ph	H	c-Hexyl

b) isolated as N-acetyl derivative

Numbering of C-atoms relates to ^{13}C NMR spectra

Scheme 1

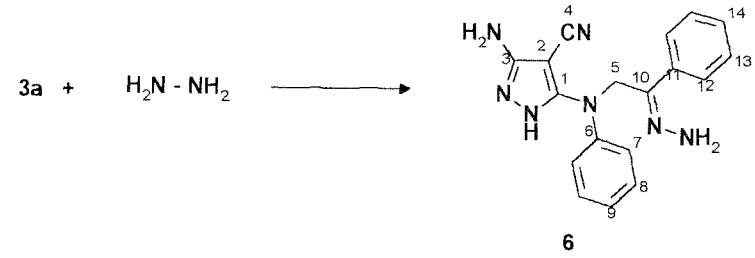
If primary amines react with **3**, it is favourable for characterization to isolate the pyrroles **5g, h** as acetyl derivatives, prepared by heating the crude product with

acetic acid anhydride. The reaction of hydrazine hydrate with **3** follows another reaction pathway. After cleavage of the oxazoline ring, hydrazine attacks the nitrile group to form a 3-amino-pyrazole; on excess of hydrazine hydrate give rise to the hydrazone **6**.

3-Amino-pyrrole **5i** was synthesized without using oxazoline **3** as intermediate; the ketene aminal **1b** reacts smoothly with chloroacetone to give immediately pyrrole **5i**.

Mercaptanes can be employed as nucleophiles to yield 3-amino-pyrroles from oxazolines **3**. For example, thiophenole reacts with **3a** to give 4-amino-5-benzoyl-1-phenyl-2-phenylthio-pyrrol-3-carbonitrile (**5j**).

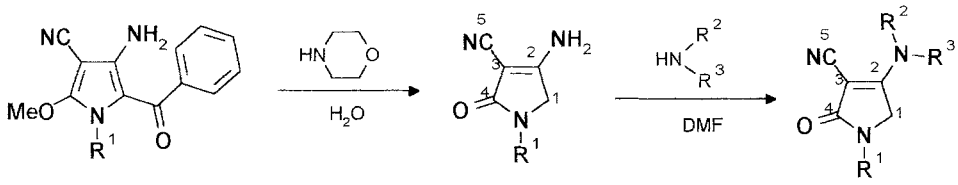
We observed that thioketene aminals **7**, obtainable from 3,3-*bis*methylthio-2-cyano-acrylic acid methyl ester and anilines, also react with α-halogenketones to give oxazolines **8** as useful intermediates for the synthesis of pyrrolines. Thioketene aminals **7** exhibit a definite structure if the formation of an intramolecular hydrogen bond is possible. Examinations employing 3-aminocrotonic acid esters revealed that the formation of such a hydrogen bond leads to a remarkable shift of the respective CO absorption band in the IR spectrum [6]. The IR absorption of **7a** with ν(CO) = 1659 cm^{-1} [7] accounts for an intramolecular hydrogen bond.



7	8	10	R^1	R^2	R^3
a	a	a	Ph	$-(CH_2)_2-O-(CH_2)_2-$	
–	–	b	Ph	$-(CH_2)_5-$	
b	b	c	p-Cl-Ph	$-(CH_2)_2-O-(CH_2)_2-$	
–	–	d	p-Cl-Ph	$-(CH_2)_5-$	

Numbering of C-atoms relates to ^{13}C NMR spectra

Scheme 2



11 12 13

11, 12	R^1
a	Ph
b	p-Cl-Ph

13	R^1	R^2	R^3
a	Ph	$-(CH_2)_2-O-(CH_2)_2-$	
b	p-Cl-Ph	$-(CH_2)_2-O-(CH_2)_2-$	
c	p-Cl-Ph	$-(CH_2)_5-$	
d	p-Cl-Ph	$-(CH_2)_4-$	

Numbering of C-atoms relates to ^{13}C NMR spectra

Scheme 3

The oxazolines **8**, possessing an exocyclic double bond, are expected to give *E/Z*-isomers, but only one of the diastereomers of **8** could be detected in the ^{13}C NMR spectra. It can be assumed that steric and electronic reasons give preference to one of the isomers; however, we were not able to prove its structure unambiguously.

Secondary amines attack the oxazoline ring of **8** at position 2 under ring cleavage. Here, the not isolable ketene aminals **9** undergo a *Dieckmann* condensation reaction, followed by β-ketoester cleavage with debenzoylation yielding the pyrrolin-3-ones **10**.

The behavior of 2-methoxy-pyrroles **11**, well known from earlier studies [1], were investigated towards substitution with secondary amines. We established loss of the benzoyl and methoxy group and obtained the 4-amino-pyrrolin-2-ones **12**. Displacement of ammonia occurs if **12** is treated under vigorous conditions with secondary amines to give the pyrrolin-2-ones **13**. Regarding the position of oxo and amino functionalities, pyrrolinones **10** and **13** are isomeric compounds. The unambiguous structural assignment of substituent positions results from the way of synthesis leading to the pyrrolin-3-ones **10**.

Experimental

Melting points were measured on a Kofler hot-stage apparatus. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ or *DMSO*-d_6 using an AC-200 Bruker spectrometer. The IR spectra were recorded on a spectrophotometer Specord 75 (Fa. Carl-Zeiss Jena). Elemental analyses were determined on an EA 1108 (Fa. Carlo Erba, Hofheim).

3-Anilino-2-cyano-3-methylthio-acrylonitrile (**1a**) and *3-methylamino-2-cyano-3-methylthio-acrylonitrile* (**1b**)

1a, **b** were prepared according to the procedures described in Refs. [1, 7a].

(3H-Oxazol-2-ylidene)-malononitrile (**3**)

3a–c were prepared according to a described procedure.

2,4-Diamino-pyrroles (**5**), *general procedure*

A solution of **3a–c** (10 mmol) in an appropriate amine (10 ml) was stirred for 1 h at an oilbath temperature of 95°C. The reaction mixture was cooled and then poured into water (100 ml). The precipitate was filtered off and recrystallized from the given solvent.

4-Amino-5-benzoyl-2-morpholin-4-yl-1-phenyl-pyrrol-3-carbonitrile (**5a**)

Starting compounds: **3a** and morpholine. Product: yellow crystals (2.1 g, 56%); m.p.: 180–182°C (*n*-propanol); ^{1}H NMR: $\delta = 3.10$ (t, 4H, $N(CH_2)_2$), 3.30 (t, 4H, $O(CH_2)_2$), 6.65 (s, 2H, NH_2), 7.00–7.25 (m, 10H, phenyl-H) ppm; IR (KBr): $\nu = 3381$, 3260 (NH_2), 2215 (CN), 1606 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (1gε) = 238 (4.43) nm; $C_{22}H_{20}N_4O_2$ (372.4); calcd.: C 70.95, H 5.52, N 15.04; found: C 70.87, H 5.47, N 15.11.

4-Amino-5-benzoyl-1-phenyl-2-piperidin-1-yl-pyrrol-3-carbonitrile (**5b**)

Starting compounds: **3a** and piperidine. Product: yellowish crystals (2.8 g, 76%); m.p.: 152–155°C (methanol); IR (KBr): $\nu = 3417$, 3317 (NH_2), 2210 (CN), 1615 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (1gε) = 241 (4.41), 276 (4.20), 352 (4.30) nm; $C_{23}H_{22}N_4O$ (370.4); calcd.: C 74.57, H 5.99, N 15.13; found: C 74.73, H 5.99, N 15.07.

4-Amino-5-benzoyl-2-dimethylamino-1-phenyl-pyrrol-3-carbonitrile (**5c**)

For the preparation of **5c**, a solution of dimethylamine in ethanol (30%) and **3c** were used and the reaction mixture was refluxed for 1 h to yield yellow-brown crystals (2.0 g, 61%).

M.p.: 151–153°C (methanol); IR (KBr): $\nu = 3392$, 3290 (NH_2), 2197 (CN), 1616 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (1gε) = 240 (4.20), 373 (3.98), 351 (4.15) nm; $C_{20}H_{18}N_4O$ (330.4); calcd.: C 72.70, H 5.50, N 16.96; found: C 73.28, H 5.56, N 17.08.

5-Acetyl-4-amino-2-morpholin-4-yl-1-phenyl-pyrrol-3-carbonitrile (**5d**)

Starting compounds: **3c** and morpholine. Product: colorless crystals (2.4 g, 75%); m.p.: 229–231°C (acetonitrile); IR (KBr): $\nu = 3290$, 3390 (NH_2), 2207 (CN), 1591 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (1gε) = 238 (4.29), 266 (4.32), 232 (4.22) nm; $C_{17}H_{18}N_4O_2$ (310.3); calcd.: C 65.79, H 5.85, N 18.05; found: C 66.16, H 5.95, N 18.28.

5-Acetyl-4-amino-1-phenyl-2-piperidin-1-yl-pyrrol-3-carbonitrile (**5e**)

Starting compounds: **3a** and piperidine. Product: colorless crystals (1.7 g, 55%); m.p.: 180–184°C (ethylacetate); IR (KBr): $\nu = 3387$, 3290 (NH_2), 2210 (CN), 1597 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (1gε) = 239 (4.18), 268 (4.16), 336 (4.21) nm; $C_{18}H_{20}N_4O$ (308.4); calcd.: C 70.10, H 6.54, N 18.17; found: C 70.33, H 6.64, N 18.31.

4-Amino-5-benzoyl-1-methyl-2-piperidin-1-yl-pyrrol-3-carbonitrile (**5f**)

Starting compounds: **3b** and piperidine. Product: yellow crystals (2.0 g, 65%); m.p.: 185–187°C (methanol); ^{1}H NMR (*DMSO*-d_6): $\delta = 2.9$ (s, 3H, CH_3), 1.6 (m, 6H, $3CH_2$), 3.3 (t, 4h, $N(CH_2)_2$), 6.6

(s, 2H, NH_2), 7.5 (m, 5H, phenyl-H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 180.0$ (s, CO), 155.1, 149.9 (s, C2, s, C4), 140.6 (s), 130.4 (d), 128.8 (d), 128.5 (d) (phenyl-C), 115.5, 114.5 (s, C1, s, C5), 69.8 (s, C3), 51.3 (t, $N(CH_2)_2$), 25.5 (t, CH_2), 23.4 (t, CH_2), 36.7 (q, CH_3) ppm; $C_{18}H_{20}N_4O$ (308.4); calcd.: C 70.10, H 6.54, N 18.17; found: C 70.12, H 6.48, N 18.20.

4-Acetylamino-5-benzoyl-2-butylamino-1-phenyl-pyrrol-3-carbonitrile (**5g**)

A solution of **3a** (10 mmol) in *n*-butylamine (20 ml) was stirred for 2 h at an oil-bath temperature of 105°C. The reaction mixture was cooled and then poured into water (100 ml). The oily precipitate was separated and heated to reflux with acetic acid anhydride (10 ml) for 3 min. The precipitate was filtered off and washed with ethanol to yield yellow crystals of **5g** (1.5 g, 38%).

M.p.: 285–288°C (dimethylformamide); ^1H NMR (*DMSO*-d_6): $\delta = 9.3$ (s, 1H, NHCO), 7.25–7.6 (m, 10 H, Phenyl-H), 6.15 (t, 1H, NH), 3.35 (m, 2H, NCH_2), 1.5–1.6 (m, 2H, CH_2) 1.45 (s, 3H, $COCH_3$), 1.2–1.3 (m, 2H, CH_2), 0.9 (t, 3H, CH_3) ppm; IR (KBr): $\nu = 3355$, 3223 (NH), 2210 (CN), 1660 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (lgε) = 355 (4.07) nm; $C_{24}H_{24}N_4O_2$ (400.5); calcd.: C 71.98, H 6.04, N 13.99; found: C 71.73, H 6.19, N 14.27.

4-Acetylamino-5-benzoyl-2-cyclohexylamino-1-phenyl-pyrrol-3-carbonitrile (**5h**)

A solution of 2.85 g (10 mmol) **3a** in cyclohexylamine (20 ml) was stirred for 2 h at an oil-bath temperature of 95°C. The reaction mixture was cooled and then poured into water (150 ml). The oily precipitate was separated and heated to reflux with acetic acid anhydride (10 ml) for 3 min. The precipitate was filtered off and washed with ethanol to yield yellow crystals of **5h** (2.8 g, 67%).

M.p.: 264–267°C (acetic acid); ^1H NMR (*DMSO*-d_6): $\delta = 9.3$ (s, 1H, NHCO), 7.3–7.6 (m, 10H, phenyl-H), 5.5 (d, 1H, NH), 3.55–3.65 (m, 1H; NCH), 1.45 (s, 3H, $COCH_3$), 1.0–1.95 (m, 10H, $(CH_2)_5$) ppm; IR (KBr): $\nu = 3353$, 3210 (NH), 2207 (CN), 1660 (CO) cm^{-1}; UV/Vis (ethanol): λ_{max} (lgε) = 356 (4.03) nm; $C_{26}H_{26}N_4O_2$ (426.5); calcd.: C 73.21, H 6.15, N 13.14; found: C 72.84, H 6.17, N 13.07.

5-Acetyl-4-amino-1-methyl-2-methylsulfanyl-pyrrol-3-carbonitrile (**5i**)

A mixture of **1b** (1.6 g, 10 mmol), chloroacetone (0.92 g, 10 mmol), and potassium carbonate (1.6 g) in dimethylformamide (20 ml) was stirred for 1 h at an oil-bath temperature of 80°C. The reaction mixture was cooled and poured into water (60 ml). The precipitate was filtered off and washed with water to yield **5i** (1.8 g, 86%).

M.p.: 154–156°C (ethanol); IR (KBr): $\nu = 3456$, 3350 (NH), 2216 (CN), 1611 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.4$ (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.85 (s, 3H, CH_3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 185.9$ (s, CO), 119.4 (s, C1), 146.3 (s, C2), 86.2 (s, C3), 137.5 (s, C4), 114.7 (s, C5), 36.1 (q, NCH_3), 29.6 (q, $COCH_3$)), 18.4 (q, SCH_3) ppm; $C_9H_{11}N_3OS$ (209.3); calcd.: C 51.65, H 5.30, N 20.08, S 15.32; found: C 51.86, H 5.33, N 20.24, S 15.33.

4-Amino-5-benzoyl-1-phenyl-2-phenylthio-pyrrol-3-carbonitrile (**5j**)

To a stirred solution of **3a** (2.8 g, 10 mmol) and sodium methylate (0.7 g, 10 mmol) in dimethylformamide (50 ml), thiophenole (5 ml) was added and the reaction mixture was stirred for 6 h at an oil-bath temperature of 100°C. After cooling, the mixture was poured into water (50 ml) and the precipitate was filtered off and washed with water to yield yellow needles (2.8 g, 72%).

M.p.: 170–172°C (*i*-propanol); IR (KBr): $\nu = 3378$, 3297 (NH), 2222 (CN), 1610 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.55$ (s, 2H, NH_2), 7.05–7.30 (m, 15H, phenyl-H) ppm; $C_{24}H_{17}N_3OS$ (395.4); calcd.: C 72.90, H 4.34, N 10.62, S 8.09; found: C 72.83, H 4.37, N 10.44, S 8.37.

3-Amino-5-(N-(2-hydrazono-2-phenyl-eth-1-yl)-N-phenyl)pyrrazol-4-carbonitrile (**6**)

A solution of **3a** (2.8 g, 10 mmol) in a mixture of hydrazine hydrate (20 ml, 80%) and ethanol (10 ml) was stirred for 2 h at an oil-bath temperature of 50°C. After cooling, water (20 ml) was added and the precipitate was filtered off and washed with water. Recrystallization from ethanol gave yellow-brown crystals (2.4 g, 73%).

M.p.: 211–213°C (ethanol); IR (KBr): ν = 3480, 3380, 3230 (NH), 2209 (CN) cm^{-1}; UV/Vis (ethanol): λ_{max} (lgε) = 230 (4.44), 310 (4.06) nm; ^{1}H NMR (*DMSO*-d_6): δ = 11.2 and 10.1 (s, 2H, NH_2), 6.5–8.0 (m, 10H, phenyl-H), 6.1 (s, 2H, NH_2), 5.9 (t, 1H, NH), 4.3 (d, 2H, NCH_2) ppm; ^{13}C NMR ($CDCl_3$/*DMSO*-d_6): δ = 151.8 (s, C1), 60.8 (s, C2), 152.0 (s, C3), 114.0 (s, C4), 37.7 (t, C5), 135.0 (s, C6), 115.0 (d, C9), 141.0 (s, C10), 146.0 (s, C11), 111.0 (d), 126.9 (d), 126.1 (d), 125.8 (d), 124.1 (d), (C7, C8, C12, C13, C14) ppm; $C_{18}H_{17}N_7$ (331.4); calcd.: C 65.24, H 5.17, N 29.59; found: C 65.21, H 5.28, N 29.81.

3-Anilino-2-cyano-3-methylthio-acrylic acid methylester (**7a**)

7a was prepared according to a described procedure from 3,3-*bis*methylthio-2-cyano-acrylic acid methylester and aniline [7].

3-(4-Chloro-anilino)-2-cyano-3-methylthio-acrylic acid methylester (**7b**)

A mixture of 4.1 g (0.02 mol) 3,3-*bis*methylthio-2-cyano-acrylic acid methylester and 2.55 g (0.02 mol) 4-chloroaniline in 20 ml absolute ethanol was heated to reflux for 4 h. After 12 h of crystallization, the product **7b** was filtered off and recrystallized from methanol to yield colorless crystals (4.5 g, 80%); m.p.: 130–132°C.

Methyl cyano-(3,5-diphenyl-3H-oxazol-2-ylidene)-acetate (**8a**)

12.4 g (50 mmol) **7a** were dissolved in a solution of potassium hydroxide (2.8 g) in methanol (40 ml) at room temperature. On addition of ether (500 ml), a precipitate formed which was filtered off and dried *in vacuo*.

A mixture of the above prepared potassium salt of **7a** (11.44 g, 40 mmol), 7.92 g (40 mmol) phenacylbromide, and 5.52 g (40 mmol) potassium carbonate in dimethylformamide (20 ml) was stirred for 30 min at 60°C. An additional amount of 7.92 g (40 mmol) phenacylbromide was dissolved in the reaction mixture, and after 30 min the mixture was poured into water (200 ml) and acidified with acetic acid. The oily precipitate was triturated with methanol and the solid was filtered off and washed with methanol to give a yellow product (7.05 g, 55%).

M.p.: 190–191°C (methanol/acetic acid); ^{1}H NMR (*DMSO*-d_6): δ = 8.3 (s, 1H, CH), 7.8–7.4 (m, 10H, phenyl-H), 3.6 (s, 3H, OCH_3) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 164.44 (s, C1), 116.29 (s, C2), 55.12 (s, C3), 161.63 (s, C4), 116.37 (d, C5), 134.77 (s, C6), 129.18 (d, C9), 144.98 (s, C10), 125.60 (s, C11), 130.00 (d, C14), 129.32 (d), 129.22 (d), 126.70 (d), 123.36 (d) (C7, C8, C12, C13), 50.70 (q, CH_3) ppm; $C_{19}H_{14}N_2O_3$ (318.3); calcd.: C 71.69, H 4.43, N 8.80; found: C 71.66, H 4.43, N 8.88.

Methyl cyano-(3-(4-chloro-phenyl)-5-phenyl-3H-oxazol-2-ylidene)acetate (**8b**)

Starting with 14.15 g (50 mmol) **7b**, the procedure described for **8a** was used to obtain **8b** (13.5 g, 96%).

M.p.: 232–234°C (methanol/dimethylformamide); ^{1}H NMR ($CDCl_3$): δ = 7.60–7.70 (d, 2H, Cl-phenyl-H), 7.3–7.55 (m, 7H, Cl-phenyl-H, phenyl-H), 7.05–7.10 (s, 1H, CH), 3.70 (s, 3H, OCH_3) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 164.69 (s, C-1), 116.55 (s, C-2), 55.74 (s, C-3), 162.10 (s, C-4), 116.81 (d, C-5), 145.42 (s, C-6), 129.15 (d, C-7), 125.92 (d, C-8), 134.96 (s, C-9), 129.71 (s, C-10),

134.08 (s, C-11), 129.64 (d, C-12), 123.75 (d, C-13), 129.56 (d, C-14), 51.15 (q, OCH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 167.41$ (s, C-1), 118.80 (s, C-2), 59.30 (s, C-3), 164.79 (s, C-4), 115.84 (d, C-5), 149.08 (s, C-6), 132.45 (d, C-7), 129.83 (s, C-8), 138.82 (s, C-9), 132.31 (s, C-10), 135.59 (s, C-11), 131.55 (d, C-12), 126.44 (d, C-13), 127.35 (d, C-14), 53.80 (q, OCH_3) ppm; $C_{19}H_{13}C1N_2O_3$ (352.8); calcd.: C 64.69, H 3.71, C1 10.05, N 7.94; found: C 64.56, H 3.75, C1 10.06, N 7.93.

2-Morpholin-4-yl-4-oxo-1-phenyl-4,5-dihydro-1H-pyrrol-3-carbonitrile (**10a**)

A solution of **8a** (9.54 g, 30 mmol) in morpholine (20 ml) was stirred for 4 h at 100°C. The morpholine was evaporated *in vacuo*, and the residue was triturated with butyl acetate for crystallization. The product **10a** was filtered off and recrystallized from acetone to yield colorless crystals (5.7 g, 71%).

M.p.: 203–206°C (acetone); ^1H NMR ($CDCl_3$): $\delta = 7.1$–7.5 (m, 5H, phenyl-H), 4.1 (s, 2H, CH_2), 3.65 (t, 4H, $O(CH_2)_2$), 3.45 (t, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 62.56$ (t, C1), 190.46 (s, C2), 77.19 (s, C3), 170.59 (s, C4), 115.36 (s, C5), 142.02 (s), 124.18 (d), 130.45 (d), 127.69 (d) (phenyl-C), 49.40 (t, $N(CH_2)_2$), 66.03 (t, $O(CH_2)_2$) ppm; $C_{15}H_{15}N_3O_2$ (269.3): calcd.: C 66.90, H 5.61, N 15.60; found: C 67.23, H 5.70, N 15.70.

4-Oxo-1-phenyl-2-piperidin-1-yl-4,5-dihydro-1H-pyrrol-3-carbonitrile (**10b**)

A solution of **8a** (6.36 g, 20 mmol) in piperidine (20 ml) was stirred for 4 h at 100°C. The piperidine was evaporated *in vacuo*, and the residue was triturated with ethyl acetate for crystallization. The product **10b** was filtered off and recrystallized from ethyl acetate to yield colorless crystals (2.3 g, 43%).

M.p.: 163–165°C (ethyl acetate); ^1H NMR ($CDCl_3$): $\delta = 7.5$–7.05 (m, 5H, phenyl-H), 4.05 (s, 2H, CH_2), 3.35 (m, 4H, $N(CH_2)_2$), 1.6–1.4 (m, 6H, $(CH_2)_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 62.44$ (t, C1), 190.67 (s, C2), 75.93 (s, C3), 170.34 (s, C4), 115.55 (s, C5), 142.62 (s), 123.88 (d), 130.16 (d), 127.10 (d) (phenyl-C), 50.50 (t, $N(CH_2)_2$), 25.51 (t, CH_2), 23.67 (t, CH_2) ppm; $C_{16}H_{17}N_3O$ (267.3); calcd.: C 71.89, H 6.41, N 15.72; found: C 71.82, H 6.48, N 15.82.

1-(4-Chloro-phenyl)-2-morpholin-4-yl-4-oxo-4,5-dihydro-1H-pyrrol-3-carbonitrile (**10c**)

A solution of **8b** (3.53 g, 10 mmol) in morpholine (10 ml) was stirred for 4 h at 100°C. The morpholine was evaporated *in vacuo*, and the residue was triturated with ethyl acetate for crystallization. The product **10c** was filtered off and recrystallized from a mixture of dimethylformamide/water to yield colorless crystals (1.3 g, 43%).

M.p.: 229–233°C (dimethylformamide/H_2O); ^1H NMR (*DMSO*-d_6): $\delta = 7.5$–7.6 (d, 2H, phenyl-H), 7.35–7.45 (d, 2H, phenyl-H), 4.25 (s, 2H, CH_2) 3.55–3.65 (m, 4H, $O(CH_2)_2$), 3.3–3.4 (m, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 61.72$ (t, C1), 190.23 (s, C2), 74.86 (s, C3), 168.95 (s, C4), 116.14 (s, C5), 140.47 (s), 130.89 (d), 129.78 (d), 125.89 (d) (phenyl-C), 49.11 (t, $N(CH_2)_2$), 65.31 (t, $O(CH_2)_2$) ppm; $C_{15}H_{14}C1N_3O_2$ (303.8); calcd.: C 59.31, H 4.65, C1 11.67, N 13.83; found: C 59.10, H 4.65, C1 11.87, N 13.83.

4-Oxo-1-(4-chloro-phenyl)-2-piperidin-1-yl-4,5-dihydro-1H-pyrrol-3-carbonitrile (**10d**)

A solution of **8b** (3.53 g, 10 mmol) in piperidine (10 ml) was stirred for 4 h at 100°C. The piperidine was evaporated *in vacuo*, and the residue was triturated with ethyl acetate for crystallization. The product **10d** was filtered off and recrystallized from ethyl acetate to yield colorless crystals (1.0 g, 33%).

M.p.: 202–206°C (ethyl acetate); ^1H-NMR (*DMSO*-d_6): $\delta = 7.45 - 7.55$ (d, 2H, phenyl-H), 7.3–7.4 (d, 2H, phenyl-H), 4.2 (s, 2H, CH_2), 3.25–3.4 (m, 4H, $N(CH_2)_2$), 1.4–1.6 (m, 6H, CH_2) ppm; ^{13}C

NMR (*DMSO*-d_6): $\delta = 61.73$ (t, C1), 190.26 (s, C2), 74.66 (s, C3), 168.97 (s, C4), 116.18 (s, C5), 141.09 (d), 130.65 (d), 129.73 (d), 125.73 (d) (phenyl-C), 50.05 (t, $N(CH_2)_2$), 25.25 (t, CH_2), 22.89 (t, CH_2) ppm; $C_{16}H_{16}ClN_3O$ (301.8); calcd.: C 63.68, H 5.34, Cl 11.75, N 13.92; found: C 63.50, H 5.37, Cl 11.98, N 13.80.

4-Amino-5-benzoyl-1-(4-chloro-phenyl)-2-methoxy-pyrrol-3-carbonitrile (**11b**)

11b was prepared analogously to a described 3-step procedure starting from 4-chloro-phenyl-isothiocyanate [1].

1) 3-(4-Chloro-anilino)-2-cyano-3-methylthio-acrylonitrile

To a stirred solution of 4-chloro-phenyl-isothiocyanate (50.0 g, 295 mmol) and malonodinitrile (19.5 g, 295 mmol) in absolute ethanol (100 ml) and dimethylformamide (20 ml), a sodium ethanolate solution (prepared from 6.9 g sodium and 120 ml absolute ethanol) was added dropwise at 10°C. After 30 min, methyliodide (41.9 g, 295 mmol) was added dropwise at room temperature, and the reaction mixture was stirred for 30 min at 60°C. The precipitate was filtered off and washed with ethanol to yield a yellow product (54.5 g, 74%); m.p.: 163–166°C.

2) 3-(4-Chloro-phenyl)-5-phenyl-3H-oxazol-2-ylidene)malononitrile

A mixture of 3-(4-chloro-anilino)-2-cyano-3-methylsulfanyl-acrylonitrile (20.0 g, 80 mmol), phenacylbromide (15.84 g, 80 mmol), and potassium carbonate (20 g) in dimethylformamide (50 ml) was stirred for 1 h at 80°C. The reaction mixture was poured into water (400 ml), and the oily precipitate was triturated with ethanol for crystallization to yield a yellowish product (8.2 g, 32%).

M.p.: 268–270°C (acetic acid); $C_{18}H_{10}ClN_3O$ (319.8); calcd.: C 67.62, H 3.15, Cl 11.09, N 13.14; found: C 67.56, H 3.33, Cl 11.87, N 13.10.

3) 4-Amino-5-benzoyl-1-(4-chloro-phenyl)-2-methoxy-pyrrol-3-carbonitrile (**11b**)

A mixture of (3-(4-Chloro-phenyl)-5-phenyl-3*H*-oxazol-2-ylidene)malononitrile (3.2 g, 10 mmol) and a sodium methanolate solution (prepared from 2.3 g sodium and 50 ml methanol) was stirred for 1 h at room temperature. The precipitate was filtered off and washed with methanol to yield colorless crystals (2.5 g, 71%).

M.p.: 184–186°C (methanol/acetonitrile); $C_{19}H_{14}ClN_3O_2$ (351.8); calcd.: C 64.87, H 4.01, Cl 10.08, N 11.94; found: C 64.93, H 4.26, Cl 10.52, N 11.95.

4-Amino-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-carbonitrile (**12a**)

A mixture of **11a** (3.05 g, 10 mmol; [1]), morpholine (10 ml), and water (1 ml) was heated to reflux for 30 min at an oil-bath temperature of 140°C. The mixture was cooled, and the crystallized product was filtered off and washed ethanol to yield colorless crystals (1.7 g, 85%).

M.p.: 225°C (dec.); ^{1}H NMR (*DMSO*-d_6): $\delta = 8.5$ (d, 2H, NH_2), 7.6 (d, 2H, phenyl-H), 7.35 (t, 2H, phenyl-H), 7.05 (t, 1H, phenyl-H), 4.55 (s, 2H, CH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 49.88$ (t, C1), 168.32 (s, C2), 72.99 (s, C3), 167.49 (s, C4), 114.78 (s, C5), 139.34 (s), 118.01 (d), 128.82 (d), 122.68 (d) (phenyl-C) ppm; $C_{11}H_9N_3O$ (199.2); calcd.: C 66.32, H, 4.55, N 21.09; found: C 66.30, H 4.59, N 21.26.

4-Amino-1-(4-chloro-phenyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-carbonitrile (**12b**)

A mixture of **11b** (1.76 g, 5 mmol), morpholine (10 ml), and water (0.5 ml) was heated to reflux for 30 min at an oil-bath temperature of 140°C. The mixture was cooled, and the crystallized product was filtered off and washed with ethanol to yield colorless crystals (1.0 g 85%).

M.p.: 300°C (dec.); ^{1}H NMR (*DMSO*-d_6): $\delta = 8.6$ (d, 2H, NH_2), 7.65 (d, 2H, phenyl-H), 7.4 (d, 2H, phenyl-H), 4.5 (s, 2H, CH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 49.78$ (t, C1), 168.30 (s, C2), 72.86 (s, C3), 167.52 (s, C4), 114.61 (s, C5), 138.24 (s), 119.40 (d), 128.61 (d), 126.29 (s) (phenyl-C) ppm; $C_{11}H_8ClN_3O$ (233.7); calcd.: C 56.54, H 3.45, Cl 15.17, N 17.98; found: C 56.72, H 3.49, Cl 15.42, N 17.80.

4-(Morpholin-4-yl)-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-carbonitrile (**13a**)

A solution of **12a** (1.99 g, 10 mmol) in morpholine (10 ml) and dimethylformamide (10 ml) was heated to reflux for 4 h at an oil-bath temperature of 180°C. All volatile components were evaporated under reduced pressure, and the residue was triturated with ethanol. The precipitate was filtered off and washed ethanol to yield colorless crystals (2.5 g, 93%).

M.p.: 259°C (dec.); ^{1}H NMR (*DMSO*-d_6): $\delta = 7.75$ (d, 2H, phenyl-H), 7.35 (t, 2H, phenyl-H), 7.10 (t, 1H, phenyl-H), 4.7 (s, 2H, CH_2), 3.9–3.7 (m, 2H, NCH_2), 3.6–3.4 (m, 2H, NCH_2), 3.8–3.7 (m, 4H, $O(CH_2)_2$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 50.01$ (t, C1), 163.91 (s, C2), 72.58 (s, C3), 167.56 (s, C4), 116.30 (s, C5), 139.08 (s), 117.86 (d), 128.80 (d), 122.88 (d) (phenyl-C), 48.01 (t), 47.45 (t) ($2NCH_2$), 65.31 (t, $O(CH_2)_2$) ppm; $C_{15}H_{15}N_3O_2$ (269.3); calcd.: C 66.90, H 5.61, N 15.60; found: C 67.06, H 5.60, N 15.80.

1-(4-Chloro-phenyl)-4-morpholin-4-yl-2-oxo-2,5-dihydro-1H-pyrrol-3-carbonitrile (**13b**)

A solution of **12b** (2.34 g, 10 mmol) in morpholine (15 ml) and dimethylformamide (15 ml) was heated to reflux for 6 h at an oil-bath temperature of 180°C. All volatile components were evaporated under reduced pressure, and the residue was triturated with ethanol. The precipitate was filtered off and washed with ethanol to yield colorless crystals (2.4 g, 79%).

M.p.: 335°C (dec.) (dimethylformamide); ^{1}H NMR (*DMSO*-d_6): $\delta = 7.75$ (d, 2H, phenyl-H), 7.4 (d, 2H, phenyl-H), 4.75 (s, 2H, CH_2), 3.9–3.8 and 3.6–3.5 (m, 4H, $N(CH_2)_2$), 3.8–3.7 (m, 4H, $O(CH_2)_2$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 50.03$ (t, C1), 163.89 (s, C2), 72.42 (s, C3), 167.66 (s, C4), 116.17 (s, C5), 138.02 (s), 119.26 (d), 128.67 (d), 126.57 (s) (phenyl-C), 47.40 (t, $N(CH_2)_2$), 65.24 (t, $O(CH_2)_2$) ppm; $C_{15}H_{14}ClN_3O_2$ (303.8); calcd.: C 59.31, H 4.65, Cl 11.67, N 13.83; found: C 59.19, H 5.04, Cl 12.22, N 13.93.

1-(4-Chloro-phenyl)-2-oxo-4-piperidin-1-yl-2,5-dihydro-1H-pyrrol-3-carbonitrile (**13c**)

A solution of **12b** (2.34 g, 10 mmol) in piperidine (15 ml) and dimethylformamide (15 ml) was heated to reflux for 6 h at an oil-bath temperature of 180°C. All volatile components were evaporated under reduced pressure, and the residue was triturated with ethanol. The precipitate was filtered off and washed with ethanol to yield colorless crystals (2.4 g, 80%).

M.p.: 292–295°C (dimethylformamide); ^{1}H NMR (*DMSO*-d_6): $\delta = 7.75$ (d, 2H, phenyl-H), 7.4 (d, 2H, phenyl-H), 4.7 (s, 2H, CH_2), 3.85 (m, 2H, NCH_2), 3.50 (m, 2H, NCH_2), 1.7 (m, 6H, $(CH_2)_3$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 50.12$ (t, C1) 163.06 (s, C2), 71.48 (s, C3), 168.05 (s, C4), 116.54 (s, C5), 138.14 (s), 119.25 (d), 128.62 (d), 126.39 (s) (phenyl-C), 49.61 (t), 4839 (t), ($2NCH_2$), 25.39 (t), 25.16 (t) ($2CH_2$), 23.05 (t, CH_2) ppm; $C_{16}H_{16}ClN_3O$ (301.8); calcd.: C 63.68, H 5.34, Cl 11.75, N 13.92; found: C 63.33, H 5.39, Cl 11.71, N 13.82.

1-(4-Chloro-phenyl)-2-oxo-4-pyrrolidin-1-yl-2,5-dihydro-1H-pyrrol-3-carbonitrile (**13d**)

A solution of **12b** (2.34 g, 10 mmol) in pyrrolidine (15 ml) and dimethylformamide (15 ml) was heated to reflux for 6 h at an oil-bath temperature of 180°C. All volatile components were evaporated under reduced pressure, and the residue was triturated with ethanol. The precipitate was filtered off and washed with ethanol to yield colorless crystals (2.5 g, 87%).

M.p.: 319–321°C (dimethylformamide); ^{1}H NMR (*DMSO*-d_6): $\delta = 7.75$ (d, 2H, phenyl-H), 7.4 (d, 2H, phenyl-H), 4.65 (s, 2H, CH_2), 3.75 (t, 2H, NCH_2), 3.5 (t, 2H, NCH_2), 2.1–1.9 (m, 4H, $(CH_2)_2$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 50.00$ (t, C1), 162.44 (s, C2), 72.00 (s, C3), 167.84 (s, C4), 117.00 (s, C5), 138.23 (s), 119.26 (d), 128.69 (d), 126.42 (s) (phenyl-C), 49.41 (t), 49.17 (t), ($2NCH_2$), 25.03 (t), 24.32 (t) (CH_2CH_2) ppm; $C_{15}H_{14}ClN_3O$ (287.8); calcd.: C 62.61, H 4.90, Cl 12.32, N 14.60; found: C 62.67, H 5.00, Cl 12.44, N 14.50.

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