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Syntheses with Pyridinium and Sulfonium Salts of Acylated β-Enaminonitriles

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Summary. Pyridinium and sulfonium salts **2a–e** which can be prepared from 3-amino-2-(α-haloacetyl)-crotonitriles and 3-amino-2-(α-halo-acetyl)-3-phenyl-acrylonitriles react with malononitrile in the presence of a base to 3-amino-2-pyridinio-phenolates **3a,b** and 3-amino-2-sulfonio-phenolates **3c–e**. In an analogous way, 3-amino-2-(diethyloxyphosphoryl)-phenol **5a** and 3-amino-2-(*p*-tolyl-sulfonyl)-phenol **5b** have been prepared. 2,3-Diamino-phenoles **6a,b** are formed from the pyridinium salts **3a,b**. The behaviour of the pyridinium salts **2a,b** towards heterocumulenes has been investigated. Cyanamide leads to the (2-amino-4-hydroxy-pyrid-3-yl)-pyridinium salt **8c**. Phenylisothiocyanate gives the 3-pyridinio-2-thioxo-pyridin-4-olates **9a,b**. Carbon disulfide gives rise to 3-pyridinio-2-thioxo-pyridin-4-olate **10** or 3-pyridinio-2-thioxo-thiopyran-4-olate **11**, depending on the substituent at the 6-position. Phenylisocyanate reacts to the pyrimidin-2,4-dione **12** with loss of N-methyl-pyridinium chloride. S-methylation of **9a** and cleavage of the pyridine moiety yields the 3-amino-2-methylthio-pyrid-4-one **14**. The structures were investigated by ^1H and ^{13}C NMR spectroscopy.

Keywords. Malononitrile; Benzoles; Pyridines; Thiophenes.

Synthesen mit Pyridinium- und Sulfoniumsalzen von acetylierten β-Enaminonitrilen

Zusammenfassung. Pyridinium- und Sulfoniumsalze **2a–e**, die aus 3-Amino-2-(α-halo-acetyl)-crotonsäurenitril und 3-Amino-2-(α-halo-acetyl)-zimtsäurenitril hergestellt werden können, reagieren mit Malonsäuredinitril in Gegenwart einer Base zu 3-Amino-2-pyridinio-phenolaten **3a,b** und 3-Amino-2-sulfonio-phenolaten **3c–e**. In Analogie wurden 3-Amino-2-(diethyloxyphosphoryl)-phenol **5a** und 3-Amino-2-(*p*-tolyl-sulfonyl)-phenol **5b** erhalten. 2,3-Diamino-phenole **6a,b** werden aus den Pyridiniumsalzen **3a,b** gebildet. Das Verhalten der Pyridiniumsalze **2a,b** gegenüber Heterokumulenen ist untersucht worden. Cyanamid führt zum (2-Amino-4-hydroxy-pyrid-3-yl)-pyridiniumsalz **8c**. Phenylisothiocyanat liefert die 3-Pyridinio-2-thioxo-pyridin-4-olate **9a,b**. In Abhängigkeit vom Substituenten in der Position 6 entsteht bei der Reaktion mit Schwefelkohlenstoff ein 3-Pyridinio-2-thioxo-pyridin-4-olat **10** oder ein 3-Pyridinio-2-thioxo-thiopyran-4-olat **11**. Phenylisocyanat reagiert zum Pyrimidin-2,4-dion **12** unter Verlust von N-Methyl-pyridiniumchlorid. S-Methylierung von **9a** und Spaltung des Pyridiniumringes ergibt das 3-Amino-2-methylthio-pyrid-4-on **14**. Die Verbindungen wurden ^1H- und ^{13}C-NMR-spektroskopisch untersucht.

Introduction

Ring closure reactions by *Thorpe-Ziegler* cyclization leading to aromatic heterocyclic systems have been repeatedly employed by us using cationic substituents as

methylene activating groups. This method supplies a facile way to amino substituted heterocycles [1–3]. Our latest investigations were aimed at conferring this procedure on the syntheses of polyfunctionalized benzenes.

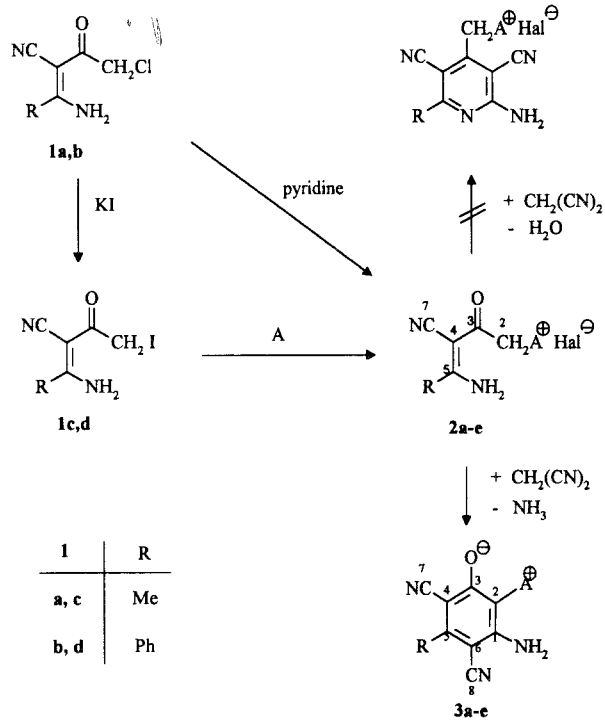
Malononitrile has been repeatedly employed in benzene ring synthesis. This transformation of pyrylium salts represents the first reported benzene forming reaction with malononitrile [4]. Later on, thiapyrylium salts have been used in this reaction [5]. Methylene group containing alkylidene malononitriles are known to react with condensation products from aldehydes or ketones and malononitrile to benzenes with the last step being an extrusion of hydrogen cyanide [6]. In a similar way enals and enons were reacted with malononitrile [7]. 1,3-Dicarbonyl compounds [8], including mono enamine derivatives [9], are also apt to form benzene derivatives with malononitrile. A complete different benzene ring synthesis with malononitrile was reported by *H. Junek* using α-methoxymethylene-β-carbonyl-carboxylic esters as starting materials [10]. For the synthesis of hexa-substituted benzenes, acylated β-enaminonitriles attracted our attention as potentially useful compounds.

Results and Discussion

The suitable starting material for our synthesis was obtained according to the published methods for compound **1a,b** [11]. Pyridine was alkylated by **1a,b** to afford 1-(4-Amino-3-cyano-2-oxo-pent-3-en-1-yl)-pyridinium chloride **2a** resp. 1-(4-Amino-3-cyano-2-oxo-4-phenyl-but-3-en-1-yl)-pyridinium chloride **2b**. **2a** and **2b** were reacted under mild conditions in a polar solvent with malononitrile and a base, preferably sodium hydroxide solution, in a two step process to the desired 3-Amino-2-pyridinio-phenolates **3a,b**. The formation of 2-Amino-pyridines could be unequivocally excluded from spectral data.

The benzene synthesis was subsequently extended to other cationic electron attracting groups at the methylene group. From preparative reasons cyclic sulfides were employed. The required iodoacetyl compounds **1c,d** for the alkylation of this sulfide could be easily obtained by a *Finkelsteĭn* reaction of **1a,b**. Other electron withdrawing groups like *p*-toluensulfonyl and phosphonic acid ester were applied for methylene group activation yielding **4a,b**. Cyclization of **4a,b** with malononitrile under basic conditions gives rise to the phenole derivatives **5a,b**.

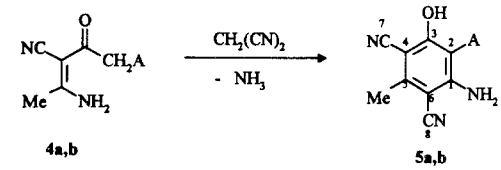
Mechanistic considerations guided us to the view that first a *Knoevenagel* reaction with liberation of ammonia occurs, followed by the intramolecular cyclization step, although no intermediate could be detected. The achievement of the aromatic status seems to be the prevailing driving force. The ^{13}C NMR chemical shifts of C-1 to C-6 in **3a–e** and **5a,b** indicate a remarkably strong alternating charge distribution (Table 1). The proton-coupled ^{13}C NMR spectra of **3a–e** and **5a,b** enable the assignment of C-2, C-4, and C-6 to the corresponding resonances due to vicinal coupling with protons of the adjacent donor groups. The singulets at position C-1 and C-3 are distinguished by the observed proton relaxation of the amino group which causes different signal intensities. Moreover, the ^{13}C NMR spectrum of **3d** in *DMSO* and 50% aqueous potassium hydroxide shows a significant downfield shift of $\Delta\delta = 8$ ppm for position C-1, indicating the possibility of an easy deprotonation of the amino group. Accordingly, no acylation could be achieved with acetic acid chloride or acetic acid anhydride.

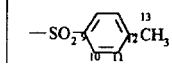


1	R
a, c	Me
b, d	Ph

2, 3	R	A	$A^{\oplus}$	$Hal^{\ominus}$
a	Me			$Cl^{\ominus}$
b	Ph			$Cl^{\ominus}$
c	Me			$I^{\ominus}$
d	Ph			$I^{\ominus}$
e	Me			$I^{\ominus}$

Scheme 1



4, 5	A
a	$PO(OEt)_2$
b	

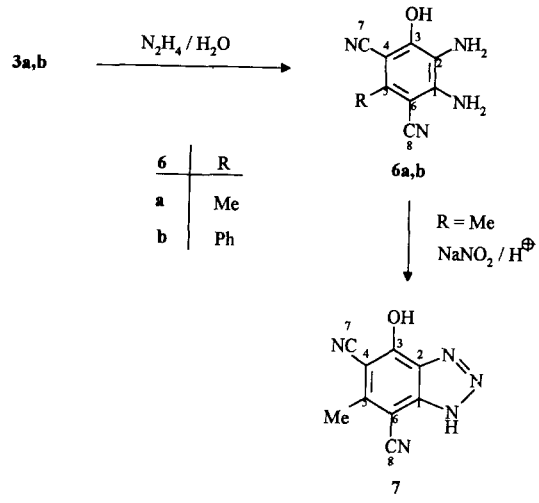
Scheme 2

Table 1. ^{13}C NMR chemical shifts and multiplicities of **2b**, **3a–e**, **5a**, **b**, **6a**, **b**, **7**, **8a–c**, **9a**, **b**, **10**, **11**, and **12** (solvent: *DMSO*-d_6)[a]

	C-1	C-2	C-3	C-4	C-5	C-6	C-7[b]	C-8[b]	other atoms
2b	–	65.94 t	186.47 (t)	78.33 m	170.98 t	–	119.19 s	–	Phenyl (*i–p*): 133.30 m, 127.98 t, 128.75 d, 131.79 t; Pyridinium (*o–p*): 146.42 m, 127.54 d, 146.21 m
3a	147.10 s	117.53 m	168.19 s	95.29 q	149.52 (q)	78.98 m	119.04 s	118.30 s	Pyridinium (*o–p*): 148.68 m, 128.42 m, 145.61 t; Me: 19.86 s
3b	153.28 s	118.26 m	166.19 s	95.10 s	147.33 t	78.86 t	118.98 s	118.34 s	Pyridinium (*o–p*): 148.73 m, 128.53 m, 145.82 t; Phenyl (*i–p*): 137.56 t, 128.56 t, 128.33 d, 128.82 t
3c	157.38 s	84.54 m	172.41 s	95.76 q	153.15 (q)	80.41 m	118.47 s	117.73 s	Thiolanium: 40.82 m, 28.93 m; Me: 20.11 s
3d	157.50 s	85.80 m	172.26 s	95.42 s	156.20 t	80.17t	118.31 s	117.72 s	Phenyl (*i–p*): 137.01 t, 128.23 t, 128.32 d, 129.07 t; Thiolanium: 40.74 m, 28.96 m
3e	157.39 s	82.30 m	173.78 s	96.14 q	153.51 (q)	80.33 m	118.27 s	117.59 s	1,4-Thioxanium: 32.96 (t); 65.24 (t); Me: 20.14 s
5a[c,d]	155.62 s	90.25 t	167.62 s	90.79 m	153.97 (q)	90.26 q	115.27 s	114.92 s	OEt: 63.42 (m), 15.95 (m); Me: 22.23 m
5b	152.87 s	107.41 s	164.10 s	92.20 p	153.93 (q)	90.28 m	115.46 s	115.16 s	(C-9 to C-13): 139.23 t, 126.93 d, 129.56 m, 144.37 (q), 21.16 t; Me: 20.40 s
6a	143.42 s	119.54 t	148.49 s	91.73 q	135.92 (q)	89.13 m	116.87 s	116.70 s	Me: 18.72 s
6b	143.13 s	121.4 br	148.18 s	91.83 s	139.58 t	89.09 t	117.13 s	116.88 s	Phenyl (*i–p*): 136.58 t, 129.51 t, 128.46 d, 128.84 t
7	138.8 br	133.87 s	158.46 s	95.03 q	147.58 (q)	86.1 br	115.15 s	114.85 s	Me: 19.83 s
8a	120.47 s	69.5 br	184.6 br	87.7 br	179.5 br	–	117.79 s	–	Phenyl (*i–p*): 138.38 m, 127.17 t, 128.30 d, 129.69 t; Pyridinium (*o–p*): 146.20 m, 127.74 m, 145.51 t
8b	155.00 s	62.27 t	170.51 (t)	87.79 m	164.62 t	–	114.71 s	–	Phenyl (*i–p*): 129.64 t, 128.79 t, 129.10 d, 132.84 t; Pyridinium (*o–p*): 146.62 m, 127.85 d, 146.49 m
8c	149.11 s	112.27 m	168.49 s	96.24 s	155.14 t	–	115.72 s	–	Phenyl (*i–p*): 131.31 t, 128.49 t, 129.21 d, 131.92 t; Pyridinium (*o–p*): 148.61 m, 129.21 m, 147.29 t
9a[e]	164.49 s	132.14 t	173.58 s	99.22 q	157.17 (q)	–	116.79 s	–	Me: 22.23 s; Pyridinium (*o–p*): 148.63 m, 127.64 d, 145.99 m; N-Phenyl (*i–p*): 141.95 t, 128.91 t, 129.14 d, 128.56 t

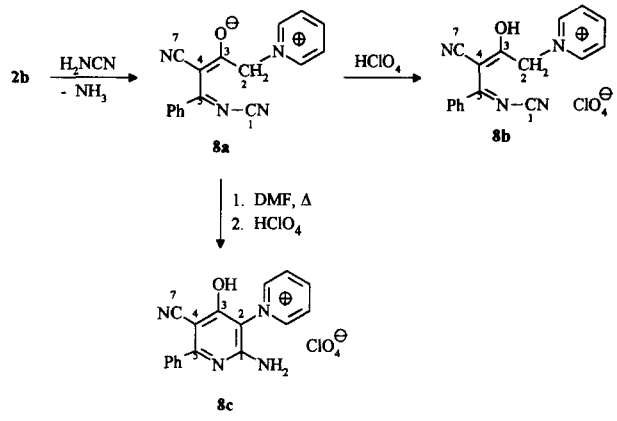
9b[e]	164.26 s	132.61 t	173.73 s	100.34 s	158.88 t	–	115.98 s	–	Phenyl (*i–p*): 133.63 t, 128.79 t, 127.90 d, 129.14 t; Pyridinium (*o–p*): 148.55 m, 127.74 d, 146.09 m; N-Phenyl (*i–p*): 141.48 t, 130.27 t, 127.90 d, 127.89 t
10[e]	169.83 s	134.1 m	165.93 s	97.24 d	156.34 m	–	116.76 s	–	Phenyl (*i–p*): 131.60 t, 128.83 t, 128.54 d, 131.06 t; Pyridinium (*o–p*): 148.52 m, 127.63 d, 146.07 m
11	176.24 s	136.81 m	167.04 s	112.00 q	166.06 (q)	–	114.50 s	–	Me: 21.22 s; Pyridinium (*o–p*): 148.10 m, 128.04 d, 146.51 m
12	149.80 s	–	160.48 s	86.97 q	162.74 (q)	–	114.87 s	–	Me: 18.47 s; N-Phenyl (*i–p*): 134.51 m, 128.90 t, 129.10 d, 128.75 t

[a]For numbering, compare corresponding formulas; data of multiplicities from ^{13}C-^{1}H coupling over three bonds without parentheses over two bonds with parentheses; [b]assignment to positions C-7 or C-8 in **3a–7** not possible; [c]multiplicities without consideration of the ^{31}P-^{13}C coupling; [d]C-1, 13.4; C-3, 13.5; C-4, 5.9; C-5, 179.5; C-6, 5.9; OCH_2CH_3, 4.8, 6.1; Me, 1.2 Hz; [e]assignment to C-1 or C-3 ambiguous



Scheme 3

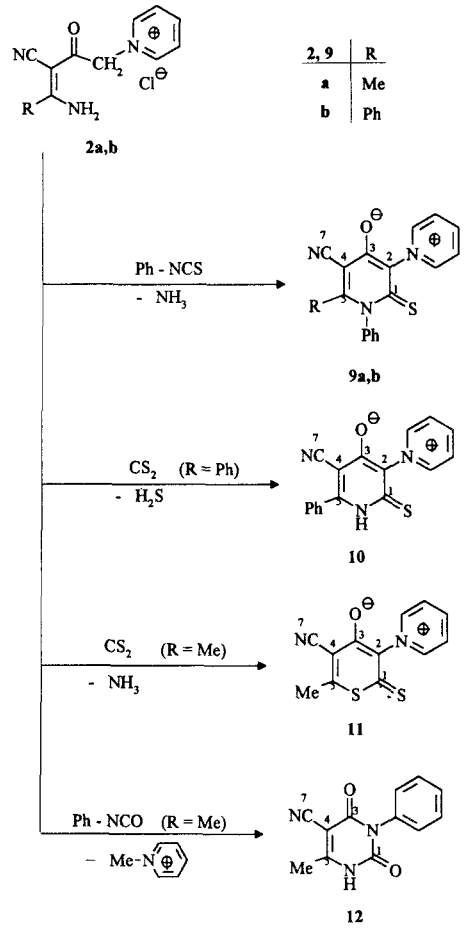
The reactivity of **3a,b** was investigated and derivatives were obtained to prove the suggested structures. *Zincke* cleavage of the pyridinium moiety by hydrazine hydrate [12] furnishes the diamino-phenole derivatives **6a** and **6b**. The *ortho* position of the amino groups was proved by diazotization of **4a** and ring closure to the benzotriazole **7**. The preferred position of the NH proton of the benzotriazole **7** was derived by comparison of the ^{13}C NMR spectra of **6a,b** and **7**.



Scheme 4

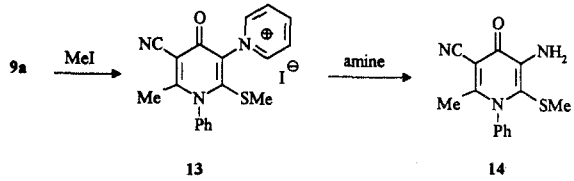
Analogously to malononitrile, cyanamide [13, 14] was reacted with **2b** to give the intermediate **8a** which could be isolated and subsequently submitted to ring closure to yield the 1-(2-Amino-5-cyano-4-hydroxy-6-phenyl-pyrid-3-yl)-pyridinium perchlorate **8c**. The structures of **8a–c** were confirmed by comparison with **2b** and assignment of the corresponding signals to $^{13}C{=}O$ and ^{13}C-OH resonances.

In the presence of a base, **2a,b** afford cyclization products with heterocumulenes. The mechanism seems to consist of an initial addition of the activated methylene group to the heterocumulene, followed by ring closure. This is indicated by the structure of the products **9a,b** to **11**. In this way the reaction of **2a,b** with phenyl isothiocyanate gives rise to the pyrid-2(1*H*)-thiones **9a,b**.



Scheme 5

The course of the reaction with carbon disulfide depends on the substituent R. In the case of **2b** (R = Ph), elimination of hydrogen sulfide and formation of the pyrid-2(1*H*)-thion **10** is observed, whereas **2a** (R = Me) affords the thiopyran-2-thione **11** by elimination of ammonia. The reaction of **2a** with phenylisocyanate apparently takes a different course, because addition of the NH_2 group of **2a** to the phenylisocyanate is followed by an attack on the carbonyl group, liberating an 1-methylpyridinium salt as leaving group to yield the pyrimidin-2,4-dion **12**. ^{13}C NMR spectra are consistent with the proposed structures **9a,b** to **12**, although C-1 and C-3 couldn't be assigned unambiguously.



Scheme 6

For further structural elucidation, **9a** was alkylated to **13** which was submitted to the *Zincke* cleavage [15, 16] of the pyridinium moiety by use of cyclohexylamine, *n*-butylamine, or hydrazinium hydrate to yield the amino derivative **14**.

In summary, it can be pointed out that acylated *β*-enaminonitriles substituted with electron-withdrawing groups of type **2** proved to be interesting intermediates for cyclization products like hexasubstituted benzenes and polyfunctionalized heterocycles.

Experimental

Melting points (uncorrected): Kofler apparatus; IR spectra (KBr-compression mould): Specord 75, Fa. Carl Zeiss Jena; UV/Vis spectra 'Cary 3' Fa. Varian Technotron Pty Limited; NMR spectra: Bruker MSL 300, *DMSO*-d_6 *TMS*; elemental analysis: Carlo Erba Instruments EA 1108-Elemental Analyser.

Iodoacetyl compounds **1a,c**, *general procedure*

15 mmol **1a** resp. **1b** (Ref. [11]) and 7.5 g powdered potassium iodide in acetone (30 ml) were heated to reflux for 2 h. The solvent was distilled off *in vacuo*, and the residue was extracted with cold water to remove inorganic salts. The product was dried and used without further purification for the next reaction step.

3-Amino-2-iodoacetyl-but-2-enenitrile (**1c**)

Colorless crystals (3.45 g, 92%), m.p. 134–137 °C (ethanol); $C_6H_7IN_2O$ (250.1); calcd.: C 28.82, H 2.82, I 50.75, N 11.20; found: C 28.94, H 2.84, I 50.63, N 11.08.

3-Amino-2-iodoacetyl-3-phenyl-acrylonitrile (**1d**)

Colorless crystals (4.4 g, 94%), m.p.: 140–142 °C (ethanol); $C_{11}H_9IN_2O$ (312.1); calcd.: C 42.33, H 2.91, I 40.66, N 8.98; found: C 42.61, H 2.92, I 41.32, N 8.61.

1-(4-Amino-3-cyano-2-oxo-pent-3-en-1-yl)-pyridinium chloride (**2a**)

3.17 g (20 mmol) **1a** and pyridine (10 ml) in *n*-butanol (15 ml) were heated to reflux for 5 min. After cooling, the precipitate was filtered by suction and washed with *n*-butanol to yield colorless crystals (3.95 g, 77%), m.p.: 302–305 °C (ethanol). ^{1}H NMR: $\delta = 2.28$ (s, 3 H, CH_3), 5.92 (s, 2 H, CH_2), 8.1–9.0 (m, 5 H, Py^+-H), 9.9 (d, 2 H, NH_2) ppm; $C_{11}H_{12}ClN_3O \cdot H_2O$ (255.7); calcd.: C 51.67, H 5.52, N 16.43, Cl 13.86; found: C 51.72, H 5.21, N 16.54, Cl 13.98.

1-(4-Amino-3-cyano-2-oxo-4-phenyl-but-3-en-1-yl)-pyridinium chloride (**2b**)

4.4 g (20 mmol) **1b** was reacted as described for **2a** to yield colorless crystals (4.95 g, 80%), m.p.: 241–244 °C (ethanol). ^{1}H NMR: $\delta = 6.08$ (s, 2 H, CH_2), 7.6–7.8 (m, 5 H, Ar-H), 8.3–9.0 (m, 5 H, Pyr^+-H), 9.75, 10.2 (2 s, 2 H, NH_2) ppm; $C_{16}H_{14}ClN_3O \cdot 0.5\ H_2O$ (308.8); calcd.: C 62.24, H 4.90, Cl 11.48, N 13.61; found: C 61.71, H 4.98, Cl 11.63, N 13.35.

S-Alkylations **2c–e**, *general procedure*

10 mmol **1c** (2.5 g) or **1d** (3.12 g) were dissolved in acetone (30 ml) and 2.64 g (30 mmol) tetrahydrothiophene or 2.08 g (20 mmol) 1,4-thioxane were added. The reaction mixture was stirred at 50 °C for 10 min

and then allowed to stand at room temperature for crystallization. The precipitate was filtered off by suction and washed with acetone. Recrystallization is not feasible due to decomposition of the sulfonium salts.

1-(4-Amino-3-cyano-2-oxo-pent-3-en-1-yl)-tetrahydrothiophenium iodide (**2c**)

Colorless crystals (2.9 g, 87%), m.p.: 136 °C (dec); $C_{10}H_{15}IN_2OS$ (338.2); calcd.: C 35.51, H 4.47, I 37.52, N 8.28, S 9.48; found: C 35.67, H 4.53, I 37.69, N 8.19, S 9.45.

1-(4-Amino-3-cyano-2-oxo-4-phenyl-but-3-en-1-yl)-tetrahydrothiophenium iodide (**2d**)

Colorless crystals (2.7 g, 68%), m.p.: 138 °C (dec); ^{1}H NMR: $\delta = 2.0$–2.4 (m, 4 H, CH_2CH_2), 3.4–3.6 (m, 2H, CH_2S^+), 4.92 (s, 2 H, CH_2S^+), 7.5–7.7 (m, 5 H, Ar-H), 9.8, 10.3 (2 s, 2 H, NH_2) ppm; $C_{15}H_{17}IN_2OS$ (400.3); calcd.: C 45.01, H 4.28, I 31.70, N 7.00, S 8.01; found: C 44.91, H 4.26, I 31.57, N 6.77, S 7.82.

4-(4-Amino-3-cyano-2-oxo-pent-3-en-1-yl)-1,4-oxathianium iodide (**2e**)

Colorless crystals (0.7 g, 20%), m.p.: 137 °C (dec); $C_{10}H_{15}IN_2O_2S \cdot 0.5$ Aceton (383.3); calcd.: C 36.04, H 4.73, I 33.11, N 7.31, S 8.37; found: C 35.75, H 4.65, I 33.95, N 7.28, S 7.46.

3-Amino-4,6-dicyano-5-methyl-2-pyridinio-phenolate (**3a**)

2.56 g (10 mmol) **2a** and 2.64 g (40 mmol) malononitrile in water (20 ml) were stirred at 40 °C, and 10 *N* sodium hydroxide solution (4 ml) was added. After 10 min of additional stirring at 40 °C, the solution was allowed to stand for 15 min at room temperature for crystallization. The precipitate was filtered off by suction and washed with water to yield yellowish crystals which were recrystallized from water (2.54 g, 98%), m.p.: 330 °C (dec); $C_{14}H_{10}N_4O \cdot H_2O$ (259.3); calcd: C 64.86, H 4.28, N 21.61; found: C 65.37, H 4.33, N 21.96.

3-Amino-4,6-dicyano-5-phenyl-2-pyridinio-phenolate (**3b**)

3.09 g (10 mmol) **2b** and 2.64 g (40 mmol) malononitrile were reacted as described for **3a** to yield colorless crystals (2.6 g, 83%), m.p.: > 360 °C (*DMF*/water); ^{1}H NMR: $\delta = 5.96$ (s, 2 H, NH_2), 7.4–7.7 (m, 5 H, Ar-H), 8.1–8.9 (m, 5 H, Pyr^+-H) ppm; $C_{19}H_{12}N_4O$ (312.3); calcd.: C 73.07, H 3.87, N 17.94; found C 72.52, H 3.97, N 17.97.

3-Amino-4,6-dicyano-5-methyl-2-(tetrahydrothiophenio)-phenolate (**3c**)

2.56 g (10 mmol) **2c** and 1.32 g (20 mmol) malononitrile were reacted as described for **3a** to yield colorless crystals after crystallization from water (2.5 g, 97%), m.p.: 240 °C (dec); ^{1}H NMR: $\delta = 6.49$ (s, 2 H, NH_2), 3.4–3.8 (m, 4 H, $(CH_2)_2S^+$), 2.4–2.9 (m, 2 H, CH_2), 2.28 (s, 3 H, CH_3), 1.8–2.2 (m, 2 H, CH_2) ppm; $C_{13}H_{13}N_3OS$ (259.3); calcd.: C 60.21, H 5.05, N 16.20, S 12.36; found C 59.80, H 5.20, N 16.13, S 12.33.

3-Amino-4,6-dicyano-5-phenyl-2-(tetrahydrothiophenio)-phenolate (**3d**)

3.09 g (10 mmol) **2d** and 5.28 g (80 mmol) malononitrile in water (20 ml) and acetonitrile (5 ml) were reacted as described for **3a** to yield colorless crystals (2.1 g, 64%) m.p.: 260–262 °C (acetonitrile/water, 1:1); ^{1}H NMR: $\delta = 2.1$ (m, 2 H, CH_2), 2.72 (m, 2 H, CH_2), 3.45–3.55 (m, 2 H, CH_2S^+), 3.7 (m, 2 H, CH_2S^+), 6.62 (s, 2 H, NH_2), 7.35–7.5 (m, 5 H, Ar-H) ppm; $C_{18}H_{15}N_3OS$ (321.4); calcd.: C 67.27, H 4.70, N 13.07, S 9.98; found: C 67.78, H 4.81, N 13.10, S 10.03.

3-Amino-4,6-dicyano-5-methyl-2-(4-oxa-thianio)-phenolate (**3e**)

2.56 g (10 mmol) **2e** and 1.32 g (20 mmol) malononitrile were reacted as described for **3a** to yield colorless needles after recrystallization from acetonitrile/water (9:1) with charcoal (1.4 g, 51%), m.p.: 270 °C; ^{1}H NMR: $\delta = 2.29$ (s, 3 H, CH_3), 3.10 (d, 2 H, CH_2S^+), 3.73 (t, 2 H, CH_2S^+), 4.34 (d, 2 H, OCH_2), 4.78 (t, 2 H, OCH_2), 6.53 (s, 2 H, NH_2) ppm; $C_{13}H_{13}N_3O_2S$ (275.3); calcd.: C 56.71, H 4.76, N 15.26, S 11.65; found: C 55.91, H 4.65, N 14.82, S 11.62.

(4-Amino-3-cyano-2-oxo-pent-3-enyl)-phosphonic acid diethyl ester (**4a**)

2.5 g (10 mmol) **1c** and 2.5 g (15 mmol) triethyl phosphite were stirred for 30 min with raising the temperature cautiously up to 100 °C for a gentle evolution of ethyl iodide. Excess of triethyl phosphite was removed *in vacuo* and the residue purified by dissolving in ethanol and precipitating with petrol ether to yield colorless crystals (2.0 g, 78%), m.p.: 114–117 °C (ethanol); $C_{10}H_{17}N_2O_4P$ (260.2); calcd.: C 46.16, H 6.58, N 10.76; found: C 46.16, H 6.67, N 10.63.

3-Amino-2-((toluen-4-sulfonyl)-acetyl)-but-2-enenitrile (**4b**)

1.58 g (10 mmol) **1a** and 2.5 g sodium *p*-toluensulfinate (90%) in absol. *DMF* (20 ml) were stirred and heated to reflux for 10 min. After cooling, water (80 ml) was added, the precipitate filtered off by suction and washed with water to yield colorless crystals after recrystallization from acetonitrile (2.4 g, 86%), m.p.: 222–225 °C (acetonitrile); ^{1}H NMR: $\delta = 2.17$ (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 4.52 (s, 2 H, CH_2), 7.43, 7.75 (m, 4 H, Ar-H), 9.5, 10.25 (2 s, 2 H, NH_2) ppm; $C_{13}H_{14}N_2O_3S$ (278.3); calcd.: C 56.10, H 5.07, N 10.07, S 11.52; found: C 56.09, H 5.14, N 10.24, S 11.49.

(2-Amino-3,5-dicyano-6-hydroxy-4-methyl-phenyl)-phosphonic acid diethyl ester (**5a**)

2.6 g (10 mmol) **4a** and 1.32 g (20 mmol) malononitrile were dissolved in absol. ethanol (5 ml). Sodium ethanolate solution, prepared from 0.5 g sodium and ethanol (10 ml) was added and the reaction mixture stirred at 50 °C for 30 min. After precipitation of the sodium salt of **5a** the solution was filtered and the product washed with a small amount of ethanol. In order to liberate **5a**, the sodium salt was dissolved in water (50 ml) and 3 *N* hydrochloric acid was added for neutralization. The precipitate was filtered off by suction and washed acid free with water to yield colorless crystals (2.8 g, 91%), m.p.: 152–153 °C (ethanol); ^{1}H NMR: $\delta = 1.25$ (t, 6 H, CH_3), 2.52 (s, 3 H, CH_3), 3.8–4.2 (m, 4 H, OCH_2), 4.0 (s, br, > 1 H, OH, HDO), 6.84 (s, 2 H, NH_2) ppm; $C_{13}H_{16}N_3O_4P$ (309.3); calcd.: C 50.49, H 5.21, N 13.59; found: C 50.62, H 5.29, N 13.65.

4-Amino-6-hydroxy-2-methyl-5-(toluen-4-sulfonyl)-isophthalonitrile (**5b**)

1.39 g (5 mmol) **4b** and 0.66 g (10 mmol) malononitrile were dissolved in ethanol (50 ml). 4 *N* potassium hydroxide solution was added and the mixture heated to reflux for 15 min. The hot solution was filtered, diluted with water (50 ml) and acidified with 3 *N* hydrochloric acid. The precipitate was filtered off by suction and washed with water to yield colorless crystals (0.85 g, 53%), m.p.: 230–233 °C (acetonitrile); ^{1}H NMR: $\delta = 2.40$ (s, 6 H, CH_3), 4.4 (s, br, > 1 H, OH, HDO), 7.39, 7.83 (2 d, 6 H, Ar-H, NH_2) ppm; $C_{16}H_{13}N_3O_3S$ (327.4); calcd.: C 58.70, H 4.00, N 12.84, S 9.78; found: C 58.75, H 4.07, N 13.02, S 9.74.

4,5-Diamino-6-hydroxy-2-methyl-isophthalonitrile (**6a**)

2.5 g (10 mmol) **3a** in *n*-propanol (5 ml) and 80% hydrazine hydrate (20 ml) was heated to reflux for 6 h. The solvents were evaporated *in vacuo*, the residue dissolved in water and acidified with 1 *N* hydrochloric acid to yield colorless crystals after recrystallization from ethanol/water (3:7) with

charcoal (0.66 g, 35%), m.p.: 280 °C (dec); $C_9H_8N_4O$ (188.2); calcd.: C 57.44, H 4.28 29.77; found: C 57.52, H 4.29, N 29.71.

4-5-Diamino-3-hydroxy-biphenyl-2,6-dicarbonitrile (**6b**)

3.12 g (10 mmol) **3b** was reacted as described for **6a** to yield nearly colorless crystals (1.8 g, 72%), m.p.: 265–268 °C (ethanol); ^{1}H NMR: $\delta = 6.2$ (s, br, > 5 H, NH_2, OH), 7.45 (s, 5 H, Ar-H) ppm; $C_{14}H_{10}N_4O$ (250.3); calcd.: C 67.19, H 4.03, N 22.39; found: C 67.56, H 4.19, N 22.54.

5,7-Dicyano-4-hydroxy-6-methyl-1H-1,2,3-benzotriazole (**7**)

0.94 (5 mmol) **6a** was dissolved in 80% sulfuric acid (20 ml). The solution was cooled to 5 °C, and under stirring a solution of aqueous sodium nitrite, prepared from 0.7 g (7 mmol) sodium nitrite and water (5 ml) was added dropwise. After 20 min of additional stirring, the reaction mixture was poured on 200 g crushed ice and the precipitate filtered off by suction to yield nearly colorless needles after recrystallization from ethanol/water (3:7) (0.64 g, 64%), m.p.: 280 °C; ^{1}H NMR: $\delta = 2.64$ (s, 3 H, CH_3), 5.5 (s, br, > 3 H, OH, NH_2) ppm; $C_9H_5N_5O$ (199.2); calcd.: C 54.27, H 2.53, N 35.16; found: C 53.89, H 2.57, N 35.37.

4-Cyanimino-3-cyano-4-phenyl-1-pyridinio-but-2-en-2-enolate (**8a**)

3.0 g (10 mmol) **2b** and 4.2 g (0.1 mol) cyanamide were dissolved in water (10 ml), and 10 *N* ammonia solution (5 ml) was added with stirring. The solution was stirred at 60 °C for 10 min and allowed to cool to room temperature during 2 h. The precipitate was filtered off by suction and washed with water to yield colorless crystals (*DHF*/water) (1.5 g, 52%), m.p.: 217 °C (dec); ^{1}H NMR: $\delta = 6.02$ (s, 2 H, CH_2), 7.35–7.65 (m, 5 H, Ar-H), 8.1–8.95 (m, 5 H, Pyr^+-H) ppm; $C_{17}H_{12}N_4O$ (288.3); calcd.: C 70.82, H 4.20, N 19.43; found: C 70.46, H 4.25, N 19.39.

1-(4-Cyanimino-3-cyano-2-hydroxy-4-phenyl-but-2-en-1-yl)-pyridinium perchlorate (**8b**)

1.44 g (5 mmol) **8a** were dissolved in 3 *N* hydrochloric acid (5 ml). With stirring, a saturated solution of sodium perchlorate (1 ml) was added and the precipitate filtered off by suction to yield colorless crystals (1.8 g, 93%), m.p.: 290–295 °C (ethanol/water); ^{1}H NMR: $\delta = 6.25$ (s, 2 H, CH_2), 8.6–8.8 (m, 5 H, Ar-H), 8.2–9.0 (m, 5 H, Pyr^+-H), 10.5–13.5 (s, br, 1 H, OH) ppm; $C_{17}H_{13}ClN_4O_5$ (388.8); calcd.: C 52.52, H 3.37, Cl 9.12, N 14.41; found: C 52.36, H 3.44, Cl 8.94, N 13.94.

1-(2-Amino-5-cyano-4-hydroxy-6-phenyl-pyrid-3-yl)-pyridinium perchlorate (**8c**)

2.88 g (10 mmol) **8a** in *DMF* (10 ml) were heated to reflux for 30 min. After cooling, the solution was diluted with water (100 ml), filtered, and perchloric acid was added for adjusting a *pH* of 6. Complete crystallization was brought about by stirring for 2 h, and the precipitate was filtered off by suction to yield colorless crystals (1.2 g, 31%), m.p.: 340 °C (dec); ^{1}H NMR: $\delta = 6.96$ (s, 2 H, NH_2), 7.65–7.8 (m, 5 H, Ar-H), 8.25–9.0 (m, 5 H, Pyr^+-H), 12.3 (s, br, 1 H, OH) ppm; $C_{17}H_{13}ClN_4O_5$ (388.8); calcd.: C 52.52, H 3.37, Cl 9.12, N 14.41; found: C 52.53, H 3.41, Cl 9.18, N 14.33.

5-Cyano-6-methyl-1-phenyl-3-pyridinio-2-thioxo-1,2-dihydro-pyridin-4-olate (**9a**)

1.2 g (5 mmol) **2a** and 1.35 g (10 mmol) phenylisothiocyanate were dissolved in ethanol (50 ml). 4 *N* potassium hydroxide solution (5 ml) was added, and the reaction mixture was heated to reflux for 15 min. After cooling, water (150 ml) was added and the solution acidified with 2 *N* hydrochloric acid inducing crystallization by stirring. The precipitate was filtered off by suction and washed with water

to yield yellow crystals (1.0 g, 59%), m.p.: 281–285 °C (acetonitrile); ^{1}H NMR: $\delta = 2.15$ (s; 3 H, CH_3), 7.25–7.55 (m, 5 H, Ar-H), 8.15–8.85 (m, 5 H, Pyr^+-H) ppm; UV/Vis (ethanol): $\lambda_{max} = 247$ (4.53), 267 (s 4.32), 305 (4.21), 382 (s 2.93) nm (lgε) $C_{18}H_{13}N_3OS \cdot H_2O$ (337.4); calcd.: C 64.07, H 4.48, N 12.45, S 9.50; found: C 64.16, H 4.05, N 12.23, S 9.13.

5-Cyano-1,6-diphenyl-3-pyridinio-2-thioxo-1,2-dihydro-pyridin-4-olate (**9b**)

0.75 g (2.5 mmol) **2b** and 0.34 g (2.5 mmol) phenylisothiocyanate were dissolved in a mixture of water (5 ml) and acetonitrile (5 ml). 10 *N* sodium hydroxide solution (1 ml) was added and the reaction mixture stirred at room temperature until a yellow precipitate formed. The reaction mixture was acidified with acetic acid, the precipitate filtered off by suction and recrystallized from acetic acid/water (4:1) to yield yellow crystals (0.45 g, 47%), m.p.: 300 °C (dec). ^{1}H NMR: $\delta = 7.1$–7.35 (m, 10 H, Ar-H), 8.15–8.95 (m, 5 H, Pyr^+-H) ppm; $C_{23}H_{15}N_3OS$ (381.5); calcd.: C 72.42, H 3.96, N 11.02, S 8.41; found C 71.53, H 3.94, N 10.86, S 8.21.

5-Cyano-6-phenyl-3-pyridinio-2-thioxo-1,2-dihydro-pyridin-4-olate (**10**)

1.5 g (5 mmol) **2b** were dissolved in a mixture of 2.3 g (30 mmol) carbon disulfide, water (5 ml) and acetonitrile (5 ml). 10 *N* sodium hydroxide solution (2 ml) was added, and the solution was stirred at room temperature for 30 min. The reaction mixture was diluted with water (50 ml), the precipitate filtered off and dried. The dried residue dissolved in *DMF* (10 ml) and triethyl amine (5 ml) was heated to reflux for 1 h. The hot solution was filtered by suction to separate the yellow precipitate. Recrystallization from glacial acetic acid afforded yellow crystals (0.92 g, 60%), m.p.: 320 °C (dec); ^{1}H NMR: $\delta = 7.55$–7.65 (m, 5 H, Ar-H), 8.15–8.95 (m, 5 H, Pyr^+-H), 12.25 (s, 1 H, NH) ppm; $C_{17}H_{11}N_3OS$ (305.4); calcd.: C 66.87, H 3.63, N 13.76, S 10.50; found: C 66.62, H 3.65, N 13.69, S 10.50.

5-Cyano-6-methyl-3-pyridinio-2-thioxo-2H-thiopyran-4-olate (**11**)

1.2 g (5 mmol) **2a** were dissolved in a mixture of 1.0 g carbon disulfide and ethanol (50 ml). After adding of 4 *N* potassium hydroxide solution (5 ml) the reaction mixture was stirred at room temperature for 1 h. The precipitate was treated with 2 *N* hydrochloric acid (15 ml), filtered off by suction and washed with water to yield yellowish crystals after recrystallization from glacial acetic acid (0.8 g, 62%), m.p.: 304–307 °C; ^{1}H NMR: $\delta = 2.49$ (s; 3 H, CH_3), 8.2–8.9 (m, 5 H, Pyr^+-H) ppm; UV (ethanol): $\lambda_{max} = 248$ (4.41), 265 (s 4.14), 320 (s 3.75) nm (lgε) $C_{12}H_8N_2OS_2$ (260.3); calcd.: C 55.36, H 3.10, N 10.76, S 24.63; found: C 55.21, H 3.09, N 10.72, S 24.67.

6-Methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-pyrimidin-5-carbonitrile (**12**)

2.4 g (10 mmol) **2a** were dissolved in a mixture of acetonitrile (30 ml) and water (30 ml). At room temperature, 1.5 g (13 mmol) phenylisocyanate and 4 *N* potassium hydroxide solution (5 ml) were successively added the solution stirred for 1 h. Then the reaction mixture was poured into water (100 ml), acidified with 2 *N* hydrochloric acid, and the precipitate filtered off by suction to yield colorless crystals (1.6 g, 70%), m.p.: 307–311 °C (methanol); ^{1}H NMR: $\delta = 2.40$ (s; 3 H, CH_3), 7.2–7.5 (m; 5 H, Ar-H), 12.5 (s; 1 H, NH) ppm; UV (ethanol): $\lambda_{max} = 276$ (4.19) nm (lgε); $C_{12}H_9N_3O_2$ (227.2); calcd.: C 63.43, H 3.99, N 18.49; found: C 63.32, H 4.04, N 18.50.

1-(5-Cyano-6-methyl-2-methylthio-4-oxo-1,4-dihydro-pyrid-3-yl)-pyridinium iodide (**13**)

1.6 g (5 mmol) **9a** and methyl iodide (5 ml) in nitromethane (30 ml) were heated to reflux for 30 min. After cooling and crystallization, the yellow precipitate was filtered off by suction and washed with nitromethane to yield yellow crystals (1.5 g, 35%), m.p.: 276 °C (dec). ^{1}H NMR: $\delta = 1.92$ (s; 3 H, CH_3),

2.42 (s; 3 H, CH_3), 7.6–7.7 (m; 5 H, Ar-H), 8.45–9.15 (m, 5 H, Pyr^+-H) ppm; UV (*DMF*): $\lambda_{max} = 304$ (s 3.91) nm (lgε) $C_{19}H_{16}IN_3OS$ (461.3); Calcd.: C 49.46, H 3.50, I 27.51, N 9.11, S 6.95; found: C 49.34, H, 3.60, I 26.60, N 9.15, S 7.07.

5-Amino-2-methyl-6-methylthio-4-oxo-1,4-dihydro-pyridin-3-carbonitrile (**14**)

1.2 g (2.5 mmol) **13** were dissolved in *DMSO* (15 ml). An amine (2 ml) like cyclohexylamine, *n*-butylamine, or hydrazine hydrate (80%) was added and the solution was heated to reflux for 30 min. After cooling, the solution was diluted with water (20 ml), the precipitate filtered off by suction and washed with water to yield yellow-brown crystals (0.5 g, 71%), m.p.: 248–250 °C (acetonitrile); ^{1}H NMR: $\delta = 2.05$ (s; 3 H, CH_3), 2.10 (s; 3 H, CH_3) 5.52 (s; 2 H, NH_2), 7.45–7.6 (m; 5 H, Ar-H) ppm; UV (ethanol): $\lambda_{max} = 336$ (4.44), 318 (4.30) nm (lgε); N-acetyl derivative: prepared by heating **14** with acetic acid anhydride; m.p.: 221–223 °C (ethanol); $C_{14}H_{13}N_3OS$ (271.3); calcd.: C 61.97, H 4.83, N 15.49, S 11.82; found: C 62.03, H 4.88, N 15.39, S 11.98.

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