SYNTHESIS, ^{1}H AND ^{13}C NMR SPECTRA, AND CONFIGURATIONAL ASSIGNMENT OF FURFURYLIDENEIMIDAZOLINONES

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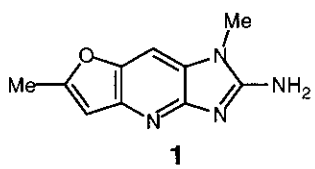
Abstract — The title compounds (**14** and **15**) were obtained by the condensation of a 2- or 3-furaldehyde derivative (prepared from 2-methylfuran) with 2-amino-1-methyl-2-imidazolin-4-one (**6**) or -5-one (**7**). Most products from **6** contained the *(E)*- and *(Z)*-isomers in comparable amounts; in those from **7**, the *(Z)*-isomer generally predominated. The isomers were distinguished by their ^{1}H and ^{13}C NMR spectra, in particular by the three-bond coupling between the carbonyl carbon and the olefinic hydrogen. This led to configurational reassignment of some previously reported analogues.

INTRODUCTION

One furfurylideneimidazolinone,[2] a few furfurylideneimidazolidinediones[3] and numerous related compounds[2–5] have been prepared from the appropriate aromatic aldehydes and heterocyclic compounds by modified Perkin[6] or, occasionally, Wittig reaction.[7] As part of a programme[8] dealing with bioactive heterocycles,[9] and with their synthesis from aromatic aldehydes and creatinine (**6**),[10] the title compounds were needed as possible intermediates in the synthesis of a naturally occurring furoimidazopyridine (**1** or a closely related isomer).[11] We also examined how various substituents in the furan ring affect the yield, the *(E/Z)*-isomeric ratio and the NMR spectra of the products.



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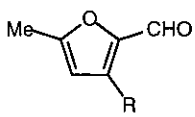
a: R = H
b: R = Br
c: R = I
d: R = NO_2



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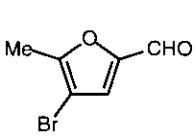
e: R = Cl
f: R = N_3
g: R = NH_2
h: R = NHBoc



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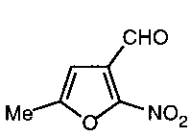

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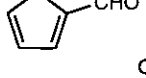

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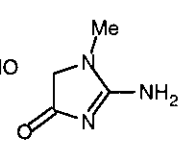

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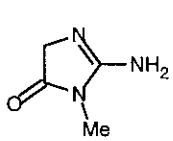

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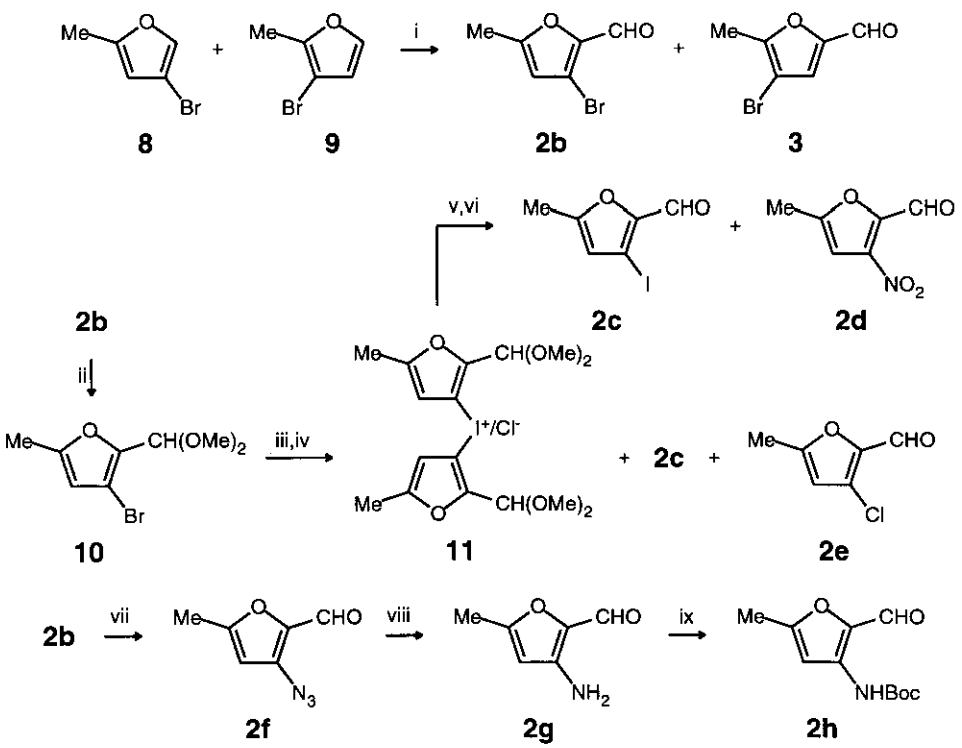
RESULTS AND DISCUSSION

For synthesis of the title compounds, we investigated the condensations of furaldehydes (**2a–h**, **3** and **4**) with 2-amino-1-methyl-2-imidazolin-4-one (creatinine, **6**) and -5-one (**7**).[12] For comparison with previously reported results,[2] the products from 2-furaldehyde (**5**) and **6** were also studied. Among the reactants, only **2a**, **5** and **6** were commercially available.

The 2-furaldehydes (**2b–h** and **3**) were prepared as shown in Scheme 1. A mixture of bromomethylfurans (**8** and **9**)[13] was obtained from 2-methylfuran. Vilsmeier formylation[14] of the mixture gave the expected aldehydes (**2b** and **3**). After chromatographic separation, the total yield was 77%.

5-Methyl-3-nitro-2-furaldehyde (**2d**) was synthesized essentially as described for 3-nitro-2-furaldehyde.[15] Thus, **2b** was converted into its dimethyl acetal (**10**) in 90% yield under mild conditions.[16] The iodonium chloride (**11**) was prepared in 27% yield from **10** by metal–halogen exchange, followed by addition of *trans*-1-chloro-2-dichloroiodoethene.[17] Haloaldehydes (**2c** and **2e**) were obtained as by-products, each in

Scheme 1



Reagents and conditions: i, DMF, $POCl_3$, rt, 15 h; ii, MeOH, $CH(OMe)_3$, NH_4NO_3, reflux, 16 h; iii, BuLi, Et_2O, N_2, −70°C, 20 min; iv, *trans*-ClCH=CHICl$_2$, PhMe, N_2, −70°C, 3 h; v, $NaNO_2$, $PhNO_2$, 100°C, 1.5 h; vi, 2 M HCl, rt, 3 h; vii, NaN_3, DMSO, 65°C, 48 h; viii, aq. NH_4SH, MeOH, 0°C, 20 min; ix, DMAP, Boc_2O, MeCN, 55°C, 30 min.

ca. 17% yield. However, **2e** was omitted from the present investigation, because it was hard to purify and inferior to **2b** and **2c** as a precursor of **1**. Finally, sodium nitrite, followed by acetal hydrolysis, converted **11** into **2c** and **2d** in modest yields.

3-Amino-5-methyl-2-furaldehyde (**2g**) was also prepared as described for its lower homologue.[18] Thus, the azido aldehyde (**2f**) was obtained in 43% yield by nucleophilic displacement of the bromine in **2b** with azide. Reduction of the azide group in **2f** gave **2g** in quantitative yield. Part of the product was converted to its *t*-butoxycarbonyl (Boc) derivative (**2h**) by di-*t*-butyl dicarbonate and 4-dimethylamino-pyridine (DMAP).[19]

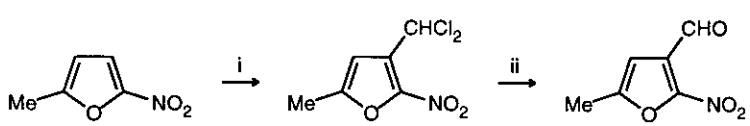
The synthesis of 5-methyl-2-nitro-3-furaldehyde (**4**) is shown in Scheme 2. A dichloromethyl group was introduced into 2-methyl-5-nitrofuran (**12**)[20] through vicarious nucleophilic substitution of hydrogen.[21] Addition of a suitable crown ether (18-crown-6) to capture the potassium counter ion of the base raised the yield of the product (**13**) to 27%, which was about twice that obtained using a literature procedure.[22] The desired nitro aldehyde (**4**) was obtained in 90% yield by silver(I) promoted hydrolysis of **13**.[22]

For easier comparison of the yields and *(E/Z)*-isomeric ratios, we prepared the title compounds under as similar conditions as possible. However, the furan ring is acid sensitive,[23] whereas the imidazolinones (**6** and notably **7**) are sensitive to alkali,[12] severely limiting the choice of catalysts. Thus, treatment of the furaldehydes (**2–5**, ArCHO) with **6** or **7** under standard Perkin conditions, i.e., heating the reactants with acetic acid, acetic anhydride and sodium acetate,[6] did not give the desired furfurylideneimidazolinones (**14** and **15**, Scheme 3). Refluxing the reactants in piperidine[4,5,24] was equally unsuccessful. Heating in various neutral solvents, such as DMF and 2-methoxyethanol, was more promising, but some aldehydes (**2f–h**) still did not react. This failure indicates excessive deactivation of the formyl group by electron release from both the furan ring and the adjacent substituent R.

With the remaining furaldehydes, heating in ethylene glycol gave the best results (Table 1). From the reaction mixtures, 20–30% of unchanged **6** could be recovered, whereas **7** was consumed completely. NMR spectral data for the products (**14** and **15**) are listed in Tables 2 and 3.

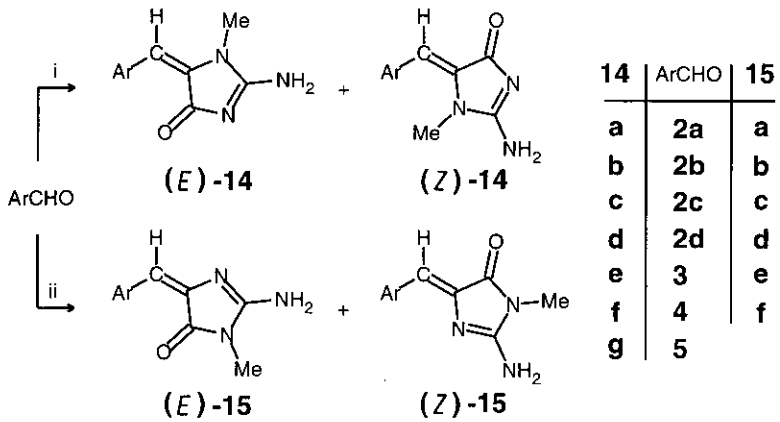
The configuration of each product was established through the spin–spin coupling constants, $^3J(^{13}C,^1H)$, across the newly formed double bond (*H*–C=C–*C*=O).[5,7] The constants were obtained from heteronuclear

Scheme 2



Reagents and conditions: i, *t*-BuOK, 18-crown-6, $CHCl_3$, DMF, THF, N_2, –70°C, 1 min; ii, aq. $AgClO_4$, PhMe, N_2, reflux, 16 h.

Scheme 3



Reagents: i, **6**, $(CH_2OH)_2$, N_2; ii, **7**, $(CH_2OH)_2$, N_2. *Conditions:* see Table 1.

multiple bond correlation (HMBC) spectra and are listed in Table 2. Apart from X-Ray crystallography, this seems to be the most reliable and general method to determine the configuration of **14**, **15** and related compounds. Another safe method, though of more limited scope, is to observe nuclear Overhauser effects

Table 1. Reaction temperature, reaction time, isomeric ratio[a] and yield of isolated product in the syntheses of the furfurylideneimidazolinones

Product	Temp. (°C)	Time (min)	*(E/Z)* ratio	Yield (%)
14a	140	120	90/10	77
14b	140	60	30/70	45
14c	140	50	25/75	60
14d	140[b]	20	50/50	20
14e	150	90	80/20	80
14f	110[b]	240	30/70	17
14g	120	20	80/20	61
15a	110	60	0/100	62
15b	110	90	0/100	67
15c	100	90	0/100	46
15d	85	90	0/100	50
15e	90	90	20/80	25
15f	110[b]	180	0/100	56

[a]Estimated by ^{1}H NMR spectroscopy. [b]First half of the time at 90°C.

Table 2. ^{1}H NMR chemical shifts (δ) and coupling constants (*J*) for the furfurylideneimidazolinones in DMSO-d_6[a]

Compound	Me	H-α	H-3'	H-4'	Me'	$J_{C,H}$ (Hz)
(E)-**14a**	3.16	6.10	7.76	6.19	2.30	8.3
(Z)-**14a**	3.41	6.22	6.64	5.96	2.15	4.6
(E)-**14b**	3.16	5.75	–	6.38	2.29	8.1
(Z)-**14b**	3.40	6.12	–	6.48	2.35	4.4
(E)-**14c**	3.15	5.73	–	6.33	2.28	7.5
(Z)-**14c**	3.39	6.16	–	6.43	2.34	4.7
(E)-**14d**	3.22	6.28	–	6.78	2.31	8.7
(Z)-**14d**	3.37	6.81	–	6.87	2.38	5.4
(E)-**14e**	3.16	6.08	7.88	–	2.29	8.6
(Z)-**14e**	3.37	6.16	6.87	–	2.32	4.3
(E)-**14f**	3.20	6.65	–	7.76	2.42	8.0
(Z)-**14f**	3.10	6.50	–	6.75	2.43	4.3
(E)-**14g**	3.17	6.14	7.84	6.56	7.68[b]	8.0
14g[c]	3.2	6.15	7.85	6.55	7.7[b]	–[d]
(Z)-**14g**	3.40	6.26	6.75	6.59	7.77[b]	4.9
(Z)-**15a**	3.03	6.20	6.91	6.21	2.30	5.2
(Z)-**15b**	3.05	6.12	–	6.44	2.33	4.8
(E)-**15c**	3.08	6.83	–	6.79	2.33	–[d]
(Z)-**15c**	3.03	6.10	–	6.38	2.31	4.3
(Z)-**15d**	3.07	6.83	–	6.81	2.33	5.7
(E)-**15e**	3.07	6.41	7.72	–	2.30	10.8
(Z)-**15e**	3.03	6.16	7.04	–	2.29	3.0
(Z)-**15f**	3.06	6.79	–	7.42	2.39	4.7

[a]Me refers to the imidazolinone moiety, 3'–5' and Me' to the furan moiety and α to the interlocking bridge. The amino group appeared at δ 7.1–8.3. $|^3J$(H-3',H-4')| = 3.2–3.5 Hz, $|^3J$(H-4',H-5')| = 1.8–1.9 Hz, $|^4J$(H-4',Me')| = 0.8–1.1 Hz; $|^3J$(H-α,C=O)| were obtained from HMBC spectra and are listed as $J_{C,H}$ in the table. [b]H-5'. [c]Data from ref. 2 without mutual assignment of H-3', H-4' and H-5'. [d]Not determined.

(NOE).[5,7] For **14**, the configurational assignments were thus confirmed by 10–15% NOE enhancement of the H-α signal in the *(E)*-isomers only, on irradiation of the *N*-methyl protons.

Some geometrical isomers were readily separated by crystallization and/or chromatography. Although *(E)*-**14e** was isolated and stored for a few days at –20°C, it slowly reverted to the original isomeric mixture. On one occasion, both isomers of **15c** were observed initially, but *(E)*-**15c** isomerized complete-

ly into *(Z)*-**15c** on brief standing at 20°C. Several attempts were made to separate the *(E)*- and *(Z)*-isomers of **14a**, **14c** or **14d**. However, the isomeric ratio always remained constant, indicating an equilibrium mixture of rapidly interconverting isomers. Such behaviour is common among isomers of this kind.[4,5,25]

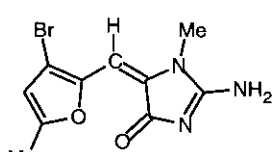
The general predominance of *(Z)*-**15** over *(E)*-**15** was clearly due to steric interference between the furan ring (Ar) and the carbonyl oxygen in the *(E)*-isomer. On the other hand, both geometrical isomers of **14** were formed, probably because *(E)*-**14** and *(Z)*-**14** are about equally crowded. Actually, the *N*-methyl group should be somewhat bulkier than the carbonyl oxygen, slightly favouring the *(E)*-isomer. *(E/Z)*-Isomeric ratios paralleling those in Table 1 have been reported for various arylidene derivatives of **6**, **7**, hydantoin and its methyl derivatives.[3–5]

The proportion of *(Z)*-**14** was higher than otherwise when the furan ring carried a substituent adjacent to the methine bridge. Such a substituent also seems to favour the *(Z)*-isomer of 5-benzylidene-1-methylhydantoins.[4,7] In the preferred conformation of *(E)*-**14** or *(Z)*-**14**, an adjacent substituent should point away from the imidazole ring and thus contribute little to the molecular strain. This is illustrated for *(E)*-**14b** and *(Z)*-**14f** by the formulas below. The observed effect of an adjacent substituent on the isomeric ratio is therefore hard to explain on steric grounds.

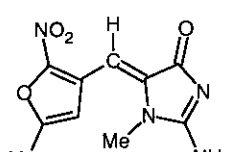
Geometrical isomers may also be distinguished by their NMR chemical shifts. Thus, an adjacent hydrogen (H-3' in **14a**, **14e**, **14g** and **15e**; Table 2) appeared at much higher frequency in the *(E)*- than in the *(Z)*-isomer, no doubt because it is, on the average, closer to the anisotropic carbonyl group. The same difference was observed between *(E)*- and *(Z)*-5-(2-furfurylidene)-1-methylhydantoin.[3] The bridge carbon (C-α) invariably appeared at higher frequency and the carbonyl carbon at lower frequency in the *(E)*-isomers of **14**, **15** (Table 3) and most related compounds[3–5] than in the respective *(Z)*-isomers. In the *(E)*-isomers of **14** and related compounds,[3] the *N*-methyl carbon always appeared at lower frequency than in the respective *(Z)*-isomers. This is probably because the molecules are nearly planar, and because the *N*-methyl carbon is closer to the aromatic ring in the *(Z)*-isomers. For the more remote *N*-methyl carbon in *(E)*- and *(Z)*-**15e**, no shift difference was observed.

However, chemical shifts are related to stereochemistry in a complex manner and should therefore be used as configurational probes with caution. Shifts for compounds like **14** and **15** may be strongly affected by the anisotropic aryl group (Ar) and, hence, by conformational changes involving rotation around the Ar–C bond. This may be one reason why most ^{1}H NMR shifts (Table 2) behave in a less regular way.

Thus, the *N*-methyl protons appeared at lower frequency in *(E)*- than in *(Z)*-**14**, probably for the same reason as the *N*-methyl carbon. However, **14f** and several related compounds[3–5] are exceptions. In



(*E*)-**14b**



(*Z*)-**14f**

Table 3. ^{13}C NMR chemical shifts (δ) for the furfurylideneimidazolinones in DMSO-d_6[a]

Compound	Me	C-2	C-4	C-5	C-α	C-2'	C-3'	C-4'	C-5'	Me'
(E)-**14a**	27.9	166.6	175.4	132.6	101.4	149.6	114.3	109.4	152.9	12.8
(Z)-**14a**	31.2	169.2	176.8	130.3	96.3	146.4	115.5	106.2	150.9	12.8
(E)-**14b**	27.6	165.9	172.4	134.4	95.2	144.8	102.5	110.7	152.6	13.6
(Z)-**14b**	32.3	169.2	176.4	131.8	92.3	144.4	104.2	111.6	154.5	13.6
(E)-**14c**	27.4	166.0	172.4	135.0	96.0	148.1	71.7	114.3	153.0	12.8
(Z)-**14c**	31.4	169.4	176.4	131.9	93.8	147.5	73.9	115.1	154.6	12.8
(E)-**14d**	27.4	166.8	172.3	140.4	93.0	148.3	136.4	102.6	152.1	12.1
(Z)-**14d**	31.6	170.0	175.9	138.1	90.3	148.1	136.8	103.4	153.3	12.1
(E)-**14e**	27.6	166.8	175.3	134.0	99.4	149.4	115.0	98.5	149.7	11.3
(Z)-**14e**	32.1	169.8	177.0	132.7	95.2	148.0	116.8	95.9	148.2	12.1
(E)-**14f**	27.7	164.4	174.5	137.9	96.5	144.6	123.4	109.7	152.6	13.3
(Z)-**14f**	31.8	167.1	175.2	136.1	94.9	144.8	122.8	110.5	153.4	13.3
(E)-**14g**	27.5	166.2	174.4	132.8	100.1	150.1	112.3	112.1	142.9	–
(Z)-**14g**	31.5	169.3	176.6	131.5	96.0	148.5	114.4	112.1	144.2	–
(Z)-**15a**	25.2	159.4	138.0	169.4	100.4	150.8	113.4	108.8	152.6	13.1
(Z)-**15b**	25.7	159.3	136.8	168.8	96.3	147.2	102.9	111.6	154.5	14.0
(Z)-**15c**	25.2	159.0	138.2	169.3	97.6	150.1	72.3	115.5	154.8	13.4
(Z)-**15d**	26.2	162.9	151.5	169.4	93.0	134.8	146.1	103.4	152.5	13.6
(E)-**15e**	25.4	156.4	135.0	164.7	107.1	149.0	115.3	99.2	151.2	11.7
(Z)-**15e**	25.4	159.6	139.1	168.6	98.3	150.5	114.8	98.5	148.6	11.3
(Z)-**15f**	25.7	161.9	148.6	168.7	97.3	146.5	127.1	111.3	155.9	13.5

[a]Me, 2, 4 and 5 refer to the imidazolinone moiety, 2'–5' and Me' to the furan moiety and α to the interlocking bridge.

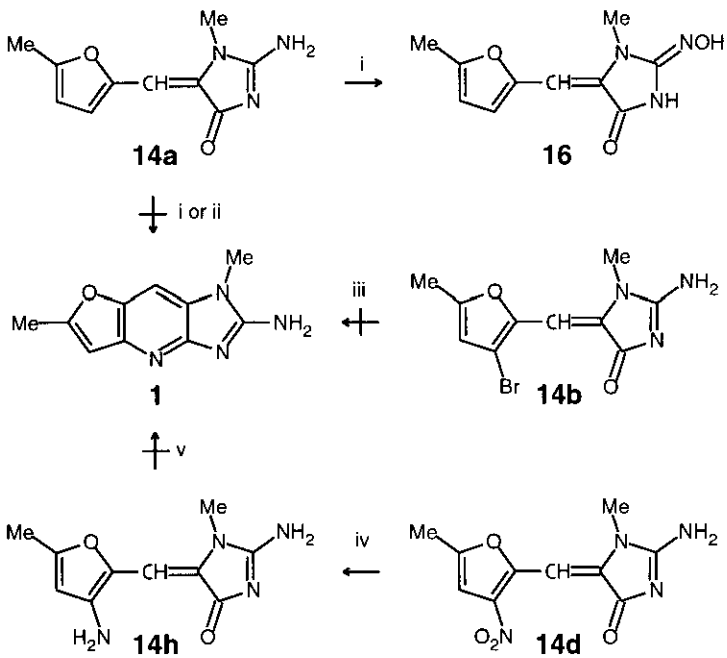
compounds closely related to **14** or **15**, the olefinic proton (H-α) generally appears at lower frequency in the *(E)*- than in the *(Z)*-isomer.[3–5] This is probably because the imidazole ring including the carbonyl group and the methine bridge is nearly planar, and because H-α is closer to the carbonyl group in the *(Z)*- than in the *(E)*-isomer. In Table 2, however, this is true only for **14a–e** and **14g**, i.e., for the products derived from a 2-furaldehyde and creatinine. A reason for the exceptional behaviour of **14f** may be that the methine bridge is flanked by an adjacent substituent and an adjacent hydrogen. This may require slight rotation around the Ar–C bond, notably in *(Z)*-**14f**.

The only furfurylideneimidazolinone for which the configuration has been determined previously seems to be *(Z)*-**14g**.[2] However, the *(Z)*-configuration was based only on the shift for H-α and a misinterpretation of the anisotropy effect exerted by the carbonyl group. A comparison of the shifts for **14g** in Table 2

with those reported[2] suggests that the latter shifts actually refer to the *(E)*-isomer. A similar investigation of the 5-benzylidenecreatinines again indicated that the reported[2] shifts refer to the *(E)*-isomer ($J_{C,H}$ 8.6 Hz) rather than the *(Z)*-isomer ($J_{C,H}$ 4.9 Hz). The configurations of the other 5-arylidenecreatinines reported in the same paper[2] should also be checked.

In order to obtain the desired furoimidazopyridine (**1**), some preliminary cyclization experiments were carried out with unseparated mixtures of geometrical isomers (Scheme 4). Thus, **14a** was treated with hydroxylamine, but this attacked the guanidine carbon rather than the carbonyl group, resulting in a diastereomeric mixture of oximes (**16**). Hydrazine hydrate did not react with **14a** at all. Attempts to substitute an amino group for the bromine in **14b** were also unsuccessful. The nitro derivative (**14d**) was readily reduced, probably to the diamine (**14h**). However, neither this reduction product nor those similarly obtained from **15d** and **15f** cyclized on heating in methanolic solution.

Scheme 4



Reagents and conditions: i, $HONH_3Cl$, pyridine, 120°C, 75 min; ii, $N_2H_4 \cdot H_2O$, $(CH_2OH)_2$, 120°C, 1 h; iii, aq. 25% NH_3, DMF or DMSO, 170°C, 15 h; iv, H_2, Raney Ni, EtOAc–MeOH, rt, 20 min; v, MeOH, reflux, 6 h.

EXPERIMENTAL

All organic solvents were of analytical grade and used as purchased. Petrol refers to petroleum ether (bp 60–70°C). Solvent mixtures are defined by volume ratios (A: petrol–EtOAc, B: cyclohexane–EtOAc,

C: $CHCl_3$–MeOH–aq. 25% NH_3). Solvents were removed by freeze-drying or by rotary evaporation at reduced pressure below 40°C. All reactions and purifications were monitored by TLC (UV detection) on aluminium sheets coated with silica gel 60 F_{254} (Merck). Flash chromatography (FC) was performed on activated basic alumina 90 (20–63 μ, Merck), silica gel (35–60 μ, Grace), or TLC-grade silica gel (2–25 μ, Aldrich), as indicated. Melting points (uncorrected) were determined on a Mettler FP62. Elemental composition was determined by HRMS. MS was performed on a JEOL JMS-SX/SX102A instrument with direct insertion, 70 eV electron impact ionization and an ion source temperature of 200°C. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX 400 at 30°C and referenced to the solvent used, $CDCl_3$ (δ 7.26 and 77.5), CD_3OD (δ 3.33), D_2O (δ 4.78), or DMSO–d_6 (δ 2.50 and 39.5). Coupling constants are given in Hz and without sign. When in doubt, assignments were confirmed by NOE difference experiments, or by gradient HMBC or heteronuclear multiple quantum coherence (HMQC) experiments. The error accumulated in the HMBC determination of $J_{C,H}$ (Table 2) did not exceed ±0.1 Hz, as shown by comparison with one-dimensional ^{13}C spectra.

Starting Materials

Compounds not listed below were commercial samples of good grade.

trans-*1-Chloro-2-(dichloroiodo)ethene*. This was prepared from iodine trichloride and acetylene.[17]

2-Amino-1-methyl-2-imidazolin-5-one (**7**). This was obtained by cyclization of glycocyamine, followed by methylation.[12]

Mixture of 4- and 3-bromo-2-methylfurans (**8** *and* **9**). This mixture was obtained from 2-methylfuran *via* its Diels–Alder adduct with maleic anhydride.[13] However, after the initial precipitation in the bromination step, the solvent was evaporated. Direct elimination of hydrogen bromide and maleic anhydride from the crude adduct saved a lot of time without affecting the yield.

2-Methyl-5-nitrofuran (**12**). This was obtained by nitration of 2-methylfuran.[20] However, the use of sodium hydrogen carbonate without any pyridine in the otherwise very exothermic elimination step simplified the procedure and nearly doubled the yield of **12** to 35%, mp 43–44.5°C (lit.,[20] 43.5°C). MS, *m/z* (rel. int.): 127 (74, M^+). ^1H NMR ($CDCl_3$): δ 2.44 (Me, dd, *J* 0.9, 0.5), 6.26 (H-4, m, *J* 3.6, 0.9), 7.24 (H-3, br d, *J* 3.6). ^{13}C NMR ($CDCl_3$): δ 13.9 (Me), 110.0 (C-4), 113.2 (C-3), 151.3 (C-5), 156.8 (C-2). A small amount (1.5%) of *2-methyl-3,5-dinitrofuran* was obtained as a by-product, mp 71–72.5°C (lit.,[26] 74°C). MS, *m/z* (rel. int.): 172 (33, M^+). ^1H NMR ($CDCl_3$): δ 2.88 (Me, d, *J* 0.5), 7.71 (H-4, q, *J* 0.5). ^{13}C NMR ($CDCl_3$): δ 14.4 (Me), 106.6 (C-4), 136.2 (C-3), 148.4 (C-5), 156.7 (C-2).

2-Furaldehydes (Scheme 1)

3- and 4-bromo-5-methyl-2-furaldehydes (**2b** *and* **3**). These were prepared essentially as described for 5-methyl-2-furaldehyde.[14] Thus, a mixture (10.0 g, 62 mmol) of 4- and 3-bromo-2-methylfurans (**8** and **9**) was poured into a stirred mixture of DMF (11 mL, 140 mmol) and phosphorus oxychloride (6.5 mL, 70 mmol) at 0°C. The mixture was left at rt overnight, then dissolved in water. The solution was neutralized

($NaHCO_3$) and extracted with *t*-butyl methyl ether. FC (A, 11:1) of the evaporation residue on silica, followed by recrystallization (MeOH) gave **2b** (4.1 g), mp 87.5–88.5°C (lit.,[27] 85–86°C), and **3** (4.9 g), mp 58.5–60°C (lit.,[28] 47°C!), corresponding to a total yield of 77%. **2b**: HRMS: calcd for $C_6H_5O_2{}^{79}Br$ (M^+) 187.9473, found 187.9456. The ^1H and ^{13}C NMR spectra were in accordance with those reported.[27] **3**: HRMS: calcd for $C_6H_5{}^{79}BrO_2$ (M^+) 187.9473, found 187.9451. ^1H NMR ($CDCl_3$): δ 2.42 (Me, d, *J* 0.4), 7.18 (H-3, q, *J* 0.4), 9.51 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 12.9 (Me), 100.1 (C-3), 124.6 (C-4), 151.4 (C-2), 157.1 (C-5), 177.0 (CHO).

3-Bromo-2-dimethoxymethyl-5-methylfuran (**10**). This was prepared essentially as described for 2,3-dibromo-5-diethoxymethylfuran.[16] Thus, **2b** (5.1 g, 27 mmol), trimethyl orthoformate (2.3 mL, 21 mmol) and ammonium nitrate (70 mg) were dissolved in dry methanol (150 mL). The solution was protected from moisture and refluxed for 16 h. After cooling, basic alumina was added and the methanol evaporated. FC (A, 6:1) of the residue on basic alumina yielded **10** (5.7 g, 90%) as a light yellow oil. MS, *m/z* (rel. int.): 234 (4, M^+). ^1H NMR ($CDCl_3$): δ 2.30 (Me-5, d, *J* 1.0), 3.41 (MeO, s), 5.36 (H-α, s), 6.03 (H-4, q, *J* 1.0). ^{13}C NMR ($CDCl_3$): δ 13.8 (Me-5), 54.3 (MeO), 97.6 (C-α), 100.5 (C-3), 110.4 (C-4), 145.7 (C-2), 153.4 (C-5).

Bis-(2-dimethoxymethyl-5-methyl-3-furyl)iodonium chloride (**11**). This was prepared essentially according to a literature procedure.[15] Thus, 1.6 M butyllithium (in hexane, 9 mL) was added within 5 min to a solution of **10** (3.10 g, 13.2 mmol) in dry ether (15 mL) at −70°C under nitrogen. After another 20 min, the mixture was added within 10 min to a solution of *trans*-1-chloro-2-dichloroiodoethene (1.80 g, 6.95 mmol) in dry toluene (12 mL) at −70°C. After another 3 h at −70°C, the mixture was allowed to reach 0°C. Water was added with stirring, until all solids had dissolved. The organic phase was saved for isolation of **2c** and **2e** (next paragraph). The aqueous phase was evaporated. Recrystallization (MeOH) of the residue yielded **11** (1.70 g, 27%), mp 130.5–132°C. ^1H NMR (D_2O): δ 2.39 (Me-5, d, *J* 0.7), 3.49 (MeO, s), 5.76 (H-α, s), 6.48 (H-4, q, *J* 0.7). ^{13}C NMR (D_2O): δ 12.2 (Me-5), 53.3 (MeO), 85.8 (C-2), 97.0 (C-α), 109.2 (C-4), 150.1 (C-3), 156.4 (C-5).

3-Iodo- and 3-chloro-5-methyl-2-furaldehydes (**2c** *and* **2e**). The organic phase obtained according to the preceding paragraph was evaporated. Fractional crystallization (petrol–EtOAc) of the residue yielded **2c** (540 mg, 17%), mp 73.5–75°C. HRMS: calcd for $C_6H_5O_2I$ (M^+) 235.9334, found 235.9326. ^1H NMR ($CDCl_3$): δ 2.41 (Me, d, *J* 0.8), 6.40 (H-4, q, *J* 0.8), 9.53 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.4 (Me), 113.5 (C-3), 118.2 (C-4), 149.8 (C-2), 160.8 (C-5), 177.1 (CHO). From the mother liquors, impure **2e** (330 mg, *ca.* 17%) was obtained. MS, *m/z* (rel. int.): 144 (25, M^+). ^1H NMR ($CDCl_3$): δ 2.39 (Me, d, *J* 0.8), 6.24 (H-4, q, *J* 0.8), 9.63 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.0 (Me), 111.3 (C-4), 129.5 (C-3), 146.3 (C-2), 159.5 (C-5), 174.9 (CHO).

5-Methyl-3-nitro-2-furaldehyde (**2d**). This was prepared from **11** (2.21 g, 4.68 mmol) as described for 3-nitro-2-furaldehyde,[15] but the intermediate acetals were not isolated. FC (A, 5:1) of the crude product on TLC-grade silica, followed by recrystallization (MeOH) yielded **2c** (110 mg, 10%; see above) and **2d** (90 mg, 12%), mp 88–89.5°C. HRMS: calcd for $C_6H_5NO_4$ (M^+) 155.0219, found 155.0188. ^1H NMR

($CDCl_3$): δ 2.47 (Me, d, *J* 0.9), 6.71 (H-4, q, *J* 0.9), 10.21 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.5 (Me), 105.3 (C-4), 110.3 (C-2), 145.9 (C-3), 158.6 (C-5), 177.2 (CHO).

3-Azido-5-methyl-2-furaldehyde (**2f**). This was prepared from **2b** (1.00 g, 5.3 mmol) as described for 3-azido-2-furaldehyde.[18] FC (A, 2:1) of the residue on silica, followed by recrystallization (MeOH) yielded **2f** (340 mg, 43%), mp 71.5–73°C. HRMS: calcd for $C_6H_5N_3O_2$ (M^+) 151.0382, found 151.0348. ^1H NMR ($CDCl_3$): δ 2.38 (Me, d, *J* 0.9), 6.17 (H-4, q, *J* 0.9), 9.52 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.8 (Me), 103.6 (C-4), 110.3 (C-2), 140.6 (CHO), 160.1 (C-5), 174.5 (C-3).

3-Amino-5-methyl-2-furaldehyde (**2g**). This was prepared from **2f** (180 mg, 1.2 mmol) as described for 3-amino-2-furaldehyde,[18] but 40% aqueous ammonium hydrogen sulfide was used rather than hydrogen sulfide. FC (A, 1:1) of the crude product on silica yielded **2g** (150 mg, 100%) as a green oil. HRMS: calcd for $C_6H_7NO_2$ (M^+) 125.0477, found 125.0441. ^1H NMR ($CDCl_3$): δ 2.27 (Me, d, *J* 0.8), 5.2 (NH_2, br s), 5.79 (H-4, q, *J* 0.8), 9.52 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.2 (Me), 101.4 (C-4), 137.9 (C-3), 147.3 (C-2), 160.3 (C-5), 167.7 (CHO).

3-(t-Butoxycarbonylamino)-5-methyl-2-furaldehyde (**2h**). This was prepared from **2g** (130 mg, 1.04 mmol) according to a literature procedure.[19] FC (A, 3:1) of the crude product on silica yielded **2h** (50 mg, 21%) as a dark oil. HRMS: calcd for $C_{11}H_{15}NO_4$ (M^+) 225.1001, found 225.0989. ^1H NMR ($CDCl_3$): δ 1.51 (Boc, s), 2.35 (Me-5, d, *J* 0.5), 6.90 (H-4, q, *J* 0.5), 8.65 (NH, br s), 9.60 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.5 (Me-5), 28.2 (CMe_3), 82.0 (CMe_3), 103.5 (C-4), 138.5 (C-3), 138.7 (C-2), 160.0 (C-5), 160.7 (NCO), 178.8 (CHO).

3-Furaldehyde **4** *(Scheme 2)*

3-Dichloromethyl-5-methyl-2-nitrofuran (**13**). A procedure[22] for dichloromethylation of 2-nitrofuran was modified as follows. A solution of **12** (1.05 g, 8.25 mmol) and dry chloroform (1.16 g, 9.7 mmol) in dry DMF (4 mL) was added dropwise to a vigorously stirred solution of 18-crown-6 (7.7 g, 29 mmol) and potassium *t*-butoxide (3.25 g, 29 mmol) in dry DMF (16 mL) and dry THF (20 mL), kept below –70°C and under nitrogen. One minute after complete addition, glacial acetic acid (4 mL) was added. The mixture was allowed to reach 0°C, poured onto ice-water and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and evaporated. Dry FC (A, 3:1) of the residue on silica, followed by FC (B, 15:1) on TLC-grade silica yielded unchanged **12** (*ca.* 300 mg, 30%) and **13** (465 mg, 27%) as a light yellow oil. HRMS: calcd for $C_6H_5NO_3Cl_2$ (M^+) 208.9646, found 208.9657. ^1H NMR ($CDCl_3$): δ 2.45 (Me, d, *J* 0.8), 6.69 (H-4, q, *J* 0.8), 7.36 ($CHCl_2$, s). ^{13}C NMR ($CDCl_3$): δ 14.1 (Me), 61.3 ($CHCl_2$), 110.0 (C-4), 128.4 (C-3), 143.4 (C-2), 155.9 (C-5).

5-Methyl-2-nitro-3-furaldehyde (**4**). This was prepared from **13** (720 mg, 3.4 mmol) as described for 2-nitro-3-furaldehyde,[22] but the refluxing was continued for 16 h. FC (A, 3:1) of the crude product on silica, followed by recrystallization (hexane–EtOAc) yielded **4** (480 mg, 90%), mp 57–60°C. HRMS: calcd for $C_6H_5NO_4$ (M^+) 155.0219, found 155.0170. ^1H NMR ($CDCl_3$): δ 2.47 (Me, d, *J* 0.8), 6.64 (H-4, q, *J* 0.8), 10.50 (CHO, s). ^{13}C NMR ($CDCl_3$): δ 14.8 (Me), 109.6 (C-3), 124.8 (C-4), 151.2 (C-2), 156.6 (C-5), 185.4 (CHO).

Furfurylideneimidazolinones (Scheme 3)

General procedure. The furaldehyde (2.00 mmol), the imidazolinone (**6** or **7**, 340 mg, 3.0 mmol) and ethylene glycol (2.0 mL) were stirred and heated under nitrogen, until TLC indicated complete reaction. The reaction times and temperatures are listed in Table 1. The mixture was cooled and freeze-dried. FC of the residue yielded one or both isomers of the desired product, or an isomeric mixture. Most products crystallized on partial evaporation of the respective fractions, but a few of them had to be recrystallized (from aq. MeOH or EtOH). All products melted with decomposition. TLC and FC were performed on silica. Unless stated otherwise, solvent mixture C (70:10:0.3) was used. Yields and isomeric ratios for the products (**14** and **15**) are listed in Table 1 and NMR spectral data in Tables 2 and 3.

2-Amino-1-methyl-5-(5-methyl-2-furfurylidene)-2-imidazolin-4-one (**14a**). FC yielded an isomeric mixture. HRMS: calcd for $C_{10}H_{11}N_3O_2$ (M^+) 205.0851, found 205.0851.

2-Amino-5-(3-bromo-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-4-one (**14b**). FC yielded *(E)*-**14b** (57 mg, 10%), mp 206–207.5°C and *(Z)*-**14b** (200 mg, 35%), mp 218–219°C. *(E)*-**14b**: HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9957. *(Z)*-**14b**: HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9985.

2-Amino-5-(3-iodo-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-4-one (**14c**). FC yielded an isomeric mixture. HRMS: calcd for $C_{10}H_{10}N_3O_2I$ (M^+) 330.9817, found 330.9762. Recrystallization (aq. MeOH) yielded *(Z)*-**14c** (140 mg, 21%), mp 207–208°C.

2-Amino-1-methyl-5-(5-methyl-3-nitro-2-furfurylidene)-2-imidazolin-4-one (**14d**). FC (C, 30:10:0.2) yielded an isomeric mixture. HRMS: calcd for $C_{10}H_{10}N_4O_4$ (M^+) 250.0702, found 250.0675.

2-Amino-5-(4-bromo-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-4-one (**14e**). FC (C, 40:10:0.3) yielded *(E)*-**14e** (340 mg, 60%), mp 234–235.5°C and *(Z)*-**14e** (113 mg, 20%), mp 260–262°C. *(E)*-**14e**: HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9951. *(Z)*-**14e**: HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9968.

2-Amino-1-methyl-5-(5-methyl-2-nitro-3-furfurylidene)-2-imidazolin-4-one (**14f**). FC yielded an isomeric mixture. HRMS: calcd for $C_{10}H_{10}N_4O_4$ (M^+) 250.0702, found 250.0684.

2-Amino-5-(2-furfurylidene)-1-methyl-2-imidazolin-4-one (**14g**).[2] FC yielded an isomeric mixture.

2-Amino-1-methyl-4-(5-methyl-2-furfurylidene)-2-imidazolin-5-one (**15a**). Recrystallization (aq. MeOH) yielded *(Z)*-**15a** (255 mg, 62%), mp 212–214°C. HRMS: calcd for $C_{10}H_{11}N_3O_2$ (M^+) 205.0851, found 205.0840.

2-Amino-4-(3-bromo-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-5-one (**15b**). Recrystallization (aq. MeOH) yielded *(Z)*-**15b** (380 mg, 67%), mp 211.5–212.5°C. HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9958.

2-Amino-4-(3-iodo-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-5-one (**15c**). FC yielded *(E)*-**15c** (150 mg, 23%), quickly converted to the *(Z)*-isomer at rt, and *(Z)*-**15c** (150 mg, 23%), mp 218–219°C. *(E)*-**15c**: HRMS: calcd for $C_{10}H_{10}N_3O_2I$ (M^+) 330.9817, found 330.9783. *(Z)*-**15c**: HRMS: calcd for $C_{10}H_{10}N_3O_2I$ (M^+) 330.9817, found 330.9763.

2-Amino-1-methyl-4-(5-methyl-3-nitro-2-furfurylidene)-2-imidazolin-5-one (**15d**). FC (C, 40:10:0.3) yielded *(Z)*-**15d** (250 mg, 50%), mp 208–209°C. HRMS: calcd for $C_{10}H_{10}N_4O_4$ (M^+) 250.0702, found 250.0677.

2-Amino-4-(4-bromo-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-5-one (**15e**). Recrystallization (aq. MeOH) yielded *(E)*-**15e** (30 mg, 5%), mp 220.5–222°C and *(Z)*-**15e** (115 mg, 20%), mp 208–209.5°C. *(E)*-**15e**: HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9954. *(Z)*-**15e**: HRMS: calcd for $C_{10}H_{10}N_3O_2{}^{79}Br$ (M^+) 282.9956, found 282.9985.

2-Amino-1-methyl-4-(5-methyl-2-nitro-3-furfurylidene)-2-imidazolin-5-one (**15f**). Recrystallization (aq. EtOH) yielded *(Z)*-**15f** (280 mg, 56%), mp 136–137°C. HRMS: calcd for $C_{10}H_{10}N_4O_4$ (M^+) 250.0702, found 250.0702.

Preliminary Cyclization Experiments (Scheme 4)

1-Methyl-5-(5-methyl-2-furfurylidene)imidazolidine-2,4-dione 2-oxime (**16**). Hydroxylammonium chloride (240 mg, 3.45 mmol) and **14a** (700 mg, 3.4 mmol) were dissolved in pyridine (30 mL) and heated in a sealed tube at 120°C for 75 min. After cooling, the reaction mixture was poured onto ice-water. The yellow precipitate was collected and washed with water and a little cold chloroform. FC (C, 30:10:0.3) of the crude product on silica yielded **16** (500 mg, 66%) as a mixture of two diastereomers, tentatively assigned the *(E)*-configuration at the oxime group. HRMS: calcd for $C_{10}H_{11}N_3O_3$ (M^+) 221.0800, found 221.0799. (2*E*,5*E*)-**16**: ^{1}H NMR (DMSO-d_6): δ 2.30 (Me', s), 3.00 (Me, s), 5.86 (H-α, s), 6.14 (H-4', d, *J* 3.4), 7.28 (H-3', d, *J* 3.4), 9.3 (NH, s), 11.4 (OH, s). (2*E*,5*Z*)-**16**: ^{1}H NMR (DMSO-d_6): δ 2.26 (Me', s), 3.31 (Me, s), 5.97 (H-α,s), 6.17 (H-4', d, *J* 2.8), 6.51 (H-3', d, *J* 2.8), 9.5 (NH, s), 11.4 (OH, s).

2-Amino-5-(3-amino-5-methyl-2-furfurylidene)-1-methyl-2-imidazolin-4-one (**14h**, *tentative structure*). Raney nickel (2 mL) was added to a solution of **14d** (100 mg, 0.40 mmol) in ethyl acetate (40 mL) and methanol (20 mL). The mixture was hydrogenated under ambient conditions for 20 min. The catalyst was removed carefully and the supernatant evaporated, yielding crude **14h** of unknown configuration. ^{1}H NMR (CD_3OD): δ 2.45 (Me', d, *J* 1.0), 2.85 (Me, s), 5.50 (H-α, s), 5.97 (H-4', q, *J* 1.0).

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