Heteroatom Chemistry
Volume 16, Number 1, 2005

One-Pot Synthesis of Pyridine Derivatives via Diels-Alder Reactions of 2,4-Dimethyl-5-methoxyoxazole

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Received 8 August 2004; revised 10 October 2004

ABSTRACT: *A novel series of pyridine derivatives with anticipated biological activity have been synthesized via Diels-Alder reactions of 2,4-dimethyl-5-methoxyoxazole with different types of dienophiles. The regioselectivity of the cycloaddition was inverted from methylacrylate to tert-butylacrylate. The structural elucidation of the new compounds was carried on the basis of spectral and X-ray analyses.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:49–55, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20064

INTRODUCTION

The Diels-Alder reaction is one of the most useful reactions in organic synthesis and is widely studied for the preparation of six-membered compounds [1]. Oxazoles have a conjugate azadiene system and are a versatile ground for investigation as the diene component in Diels-Alder reactions [2–6]. Thus thermal reaction of oxazoles with acetylenes leads to furans, while addition to olefins produces substituted pyridines [7]. In a few instances, the Diels-Alder adduct was isolated [8,9] but in most cases the primary adduct was not isolable and instead underwent rearrangement [10,11]. The methodology was applied to the synthesis of natural products (e.g. antitumor agent ellipticine [12], pyridoxal and pyridoxyl alkaloids [13]), the most famous being the synthesis of vitamin B_6 [14–16]. Recently, we added the photochemical cycloaddition of 5-methoxyoxazoles to aldehydes and α-keto esters to give bicyclic oxetanes that were used as a precursor for the stereoselective synthesis of *erythro* α-amino-β-hydroxy carboxylic acid derivatives [17,18] and *erythro* β-hydroxy dimethyl aspartates [19], respectively. The present paper deals with the regioselectivity of the reaction of 2,4-dimethyl-5-methoxyoxazole with different types of acyclic as well as cyclic dienophiles and with its application to the synthesis of analog of vitamin B_6.

RESULTS AND DISCUSSION

In order to test the regioselectivity of the Diels-Alder reaction, we used 2,4-dimethyl-5-methoxyoxazole (**1**) as an electron-rich diene and acrylonitrile, acrylaldehyde, acrylic acid, methylacrylate, *tert*-butylacrylate, *E*-crotonaldehyde, 2-butene-1,4-diol, and dimethylmaleate were applied as acyclic dienophiles. In addition to, maleic anhydride, *N*-methylmaleimide, *N*-(2-methylphenyl) maleimide, *N*-(2-carboxylphenyl) maleimide, maleimylglycine, maleimylalanine, benzoquinone, and naphthoquinone were used as cyclic dienophiles. 2,4-Dimethyl-5-methoxyoxazole (**1**) was easily synthesized in 75% yield, from the reaction of *N*-acetylalanine methylester with phosphorous pentachloride as reported earlier by us in the literature [17,18].

The reaction of 2,4-dimethyl-5-methoxyoxazole **1** with acrylic acid derivatives in boiling benzene

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afforded 3-hydroxy-2,6-dimethyl-4-substitued pyridine derivatives (**2–5**) in quantitative yield (Scheme 1). In a similar manner, compound **1** reacted with *E*-crotonalaldehyde under the same experimental conditions and gave 3-hydroxy-2,5,6-trimethylpyridine-4-carboxylaldehyde (**7**) in good yield. When compound **1** was heated in benzene with dimethylmaleate, dimethyl 5-hydroxy-2,6-dimethylpyridine-3,4-dicarboxylate (**8**) was formed in moderate yield. Treatment of 2-buten-1,4-diol with 2,4-dimethyl-5-methoxyoxazole (**1**) in refluxing benzene furnished 4,5-bis(hydroxymethyl)-2,6-dimethylpyridine-3-ol (**9**) as analog of vitamin B_6. Surprisingly, when compound **1** was heated in benzene with *tert*-butylacrylate as a bulky dienophile, the regioselectivity inversed and *tert*-butyl 5-hydroxy-2,6-dimethylpyridine-3-carboxylate (**6**) was formed in good yield.

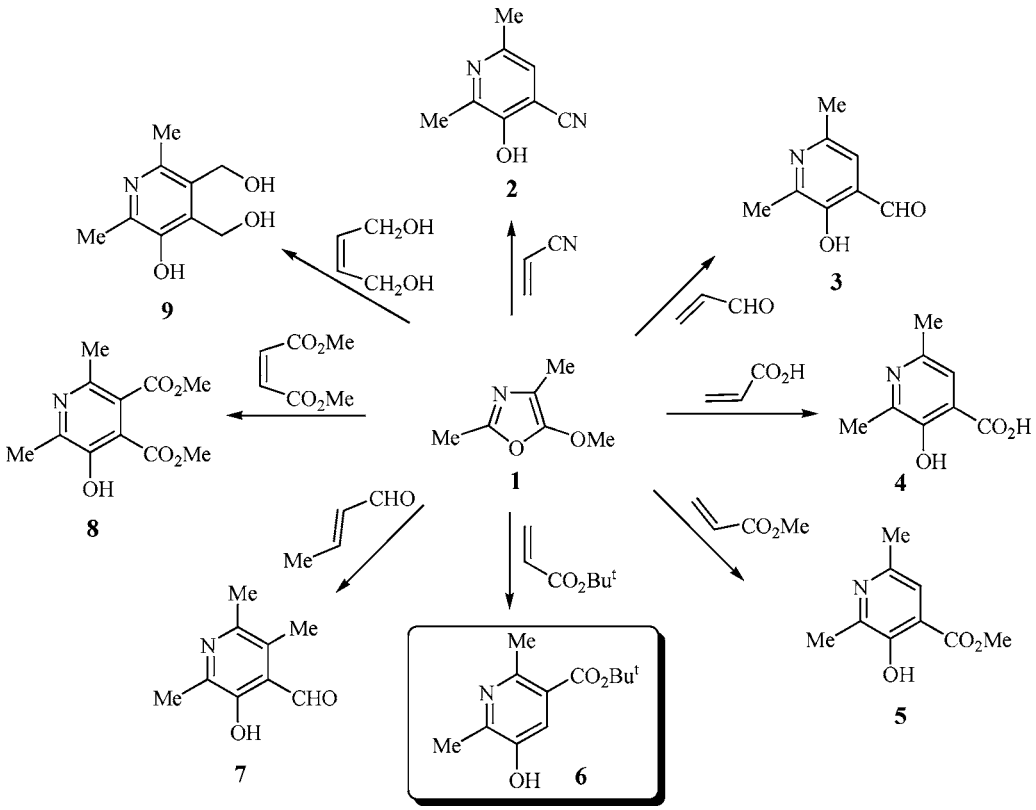
The structural confirmation of compounds **2–9** was accomplished on the basis of the analytical data and spectroscopic properties. The IR spectra showed absorption bands at 3455, 1620, 1530 cm^{-1} corresponding to the OH, C=N, C=C groups of pyridine ring, respectively. Compounds **3, 4, 5, 7**, and **8** showed additional band around 1660 cm^{-1} characteristic for C=O group. Their ^{1}H-NMR spectra displayed three singlet signals at δ 2.55, 2.59 and 7.64 ppm for two methyl groups ($2CH_3$) and one methine proton (CH=) of the pyridine ring, respectively. The mass spectrum of compound **5** revealed a strong molecular ion peak at 181 M^+.

The regioselectivity of compounds **5** and **6** was unambiguously determined by X-ray crystallographic analysis.

The low wave number of the carbonyl group ascribed to the participation in a chelated hydrogen bond with the 3-hydroxyl group as clearly proved by single crystal X-ray analysis of compound **5** (see Fig. 1).

Although the number of studies of the regioselectivity of the Diels-Alder reaction of oxazoles with unsymmetrical olefinic dienophiles is limited, the generalization has been made that the strongest electron-withdrawing substituents are found at position C-4 of the pyridyl products. The deviation of *tert*-butylacrylate may be rationalized by the steric hindrance of *tert*-butyl group when compared with CN, CHO, CO_2H, and CO_2Me groups.

Furthermore, in order to explore the synthetic utility of the [4 + 2] cycloaddition reactions of 2,4-dimethyl-5-methoxyoxazole (**1**), we have also investigated the thermal [4 + 2] cycloaddition of compound



SCHEME 1 Diels-Alder reactions of 2,4-dimethyl-5-methoxyoxazole with acyclic dienophiles.

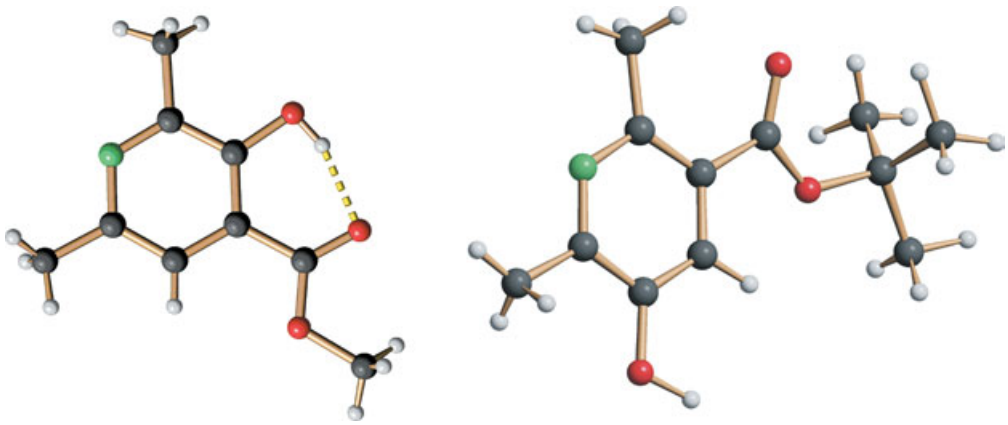
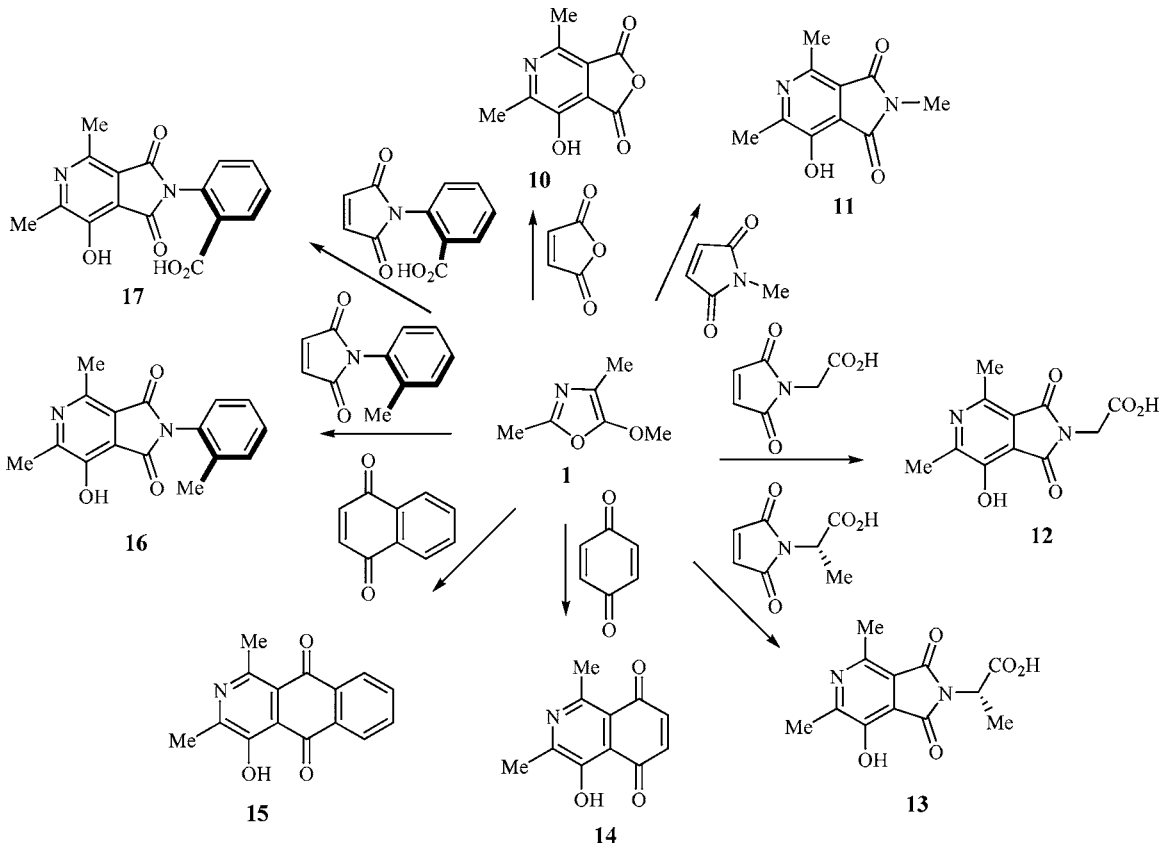


FIGURE 1 X-ray structures of compounds **5** and **6**.

1 with a series of cyclic dienophiles aiming to construct a fused heterocycles incorporating pyridine moiety with anticipated biological activity.

2,4-Dimethyl-5-methoxyoxazole (**1**) reacted with maleic anhydride in boiling benzene to form 7-hydroxy-4,6-dimethylfuro[3,4-*c*]pyridine-1,3-dione (**10**) after cleavage of the oxygen bridge of the adduct. The IR spectrum of compound **10** shows two strong bands at 1868 and 1792 cm^{-1}, assignable to C=O groups of a five-membered cyclic anhydride. 7-Hydroxy-2,4,6-trimethyl-2H-pyrrolo-[3,4-*c*]pyridine-1,3-dione (**11**) could also be obtained in a similar manner via the reaction of compound **1** with *N*-methylmaleimide in 92% yield. In view of



SCHEME 2 Diels-Alder reactions of 2,4-dimethyl-5-methoxyoxazole with cyclic dienophiles.

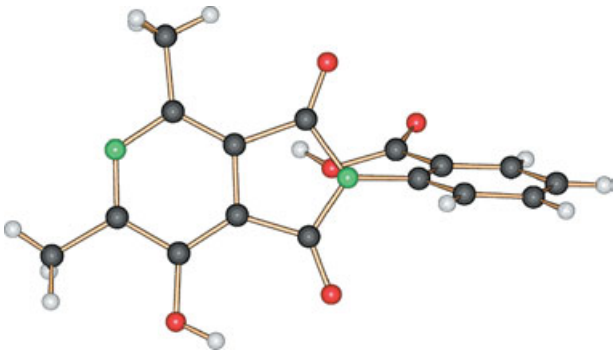


FIGURE 2 X-ray structure of compound **17**.

the simplicity of the "one-pot" synthesis of pyrrolo[3,4-*c*]pyridine derivatives (**11**), pyrrolo[3,4-*c*]pyridine derivatives **12** (92%) and **13** (70%) were both prepared using maleimylglycine and maleimylalanine under the same experimental condition. Also, compound **1** reacted with benzoquinone and naphthoquinone in benzene at reflux in a "one-pot" reaction yielding the 4-hydroxy-1,3-dimethylisoquinoline-5,8-dione (**14**) and 4-hydroxy-1,3-dimethylbenzo[*g*]isoquinoline-5,10-dione (**15**), respectively in quantitative yields as shown in Scheme 2.

We have also investigated atroposelective cycloaddition of both *N*-(2-methylphenyl) maleimide and *N*-(2-carboxylphenyl) maleimide to 2,4-dimethyl-5-methoxyoxazole. When compound **1** was heated in benzene at reflux in the presence of *N*-(2-methylphenyl) maleimide and/or *N*-(2-carboxylphenyl) maleimide, the 7-hydroxy-4,6-dimethyl-2-*o*-tolyl-2*H*-pyrrolo[3,4-*c*]pyridine-1,3-dione (**16**) and/or 2-(7-hydroxy-4,6-dimethyl-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridin-2(3*H*)-yl)benzoic acid (**17**) was formed, respectively in good yield. The chemical structure of compound **17** was unequivocally determined by single crystal X-ray analysis as depicted in Fig. 2.

Unfortunately, the optical rotation measurement of compound **17** was $[\alpha]_D^{25} = 0^\circ$ ($c = 0.05$, $CHCl_3$). We believe that the reaction seems to be nonselective and hence we have obtained a racemic mixture of atropisomers of compound (**17**). These experiments teach us that compounds **16** and **17** incorporating *N*-2-methylphenyl and *N*-2-carboxylphenyl maleimides have substantial barrier to interconversion of atropisomer (20–25 kcal/mol) but these barriers are still too low for most practical synthetic applications. All new pyridine derivatives gave satisfactory spectral and microanalytical data and/or high-resolution mass spectra.

The mechanistic scenario for formation of the 3-hydroxypyridine derivatives (**C**) may be rationalized as follows: olefinic dienophiles cycloadded to 2,4-dimethyl-5-methoxyoxazole to form the initial cycloadduct (**A**) that will be cleaved to zwitterion (**B**) followed by aromatization. The aromatization takes place via loss of methanol as depicted in Scheme 3.

In conclusion, we have demonstrated a simple "one-pot" synthesis of a number of substituted pyridine derivatives of biological significance in excellent yields via Diels-Alder reactions of 2,4-dimethyl-5-methoxyoxazole with different types of dienophiles. The regioselectivity of the cycloaddition was inverted from methylacrylate to *tert*-butylacrylate.

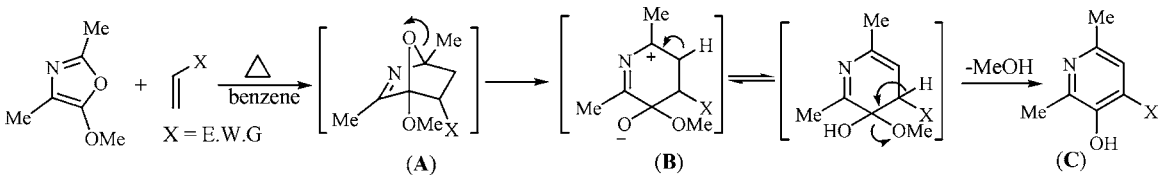
EXPERIMENTAL

All melting points were determined with a Büchi melting point apparatus (type Nr. 535) and are uncorrected. IR spectra were recorded for KBr disk on a Mattson 5000 FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker AC 300 (300 MHz) in $CDCl_3$ and/or CD_3SOCD_3 as solvent, using TMS as an internal standard, and chemical shifts are expressed as δ_{ppm}. Mass spectra were determined on Finnigan Incos 500. Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University.

2,4-Dimethyl-5-methoxyoxazole (**1**) [17,18], maleimylglycine [20], maleimylalanine [20], *N*-(2-methylphenyl) maleimide [21], and *N*-(2-carboxylphenyl)maleimide [21] were prepared according to the reported methods; the other dienophiles were commercially available.

General Procedure for the Preparation of the Pyridine Derivatives

A mixture of 2,4-dimethyl-5-methoxyoxazole (0.64 g, 0.005 mole) and dienophiles (0.005 mole) in 25 mL



SCHEME 3 Mechanistic scenario for the formation of 3-hydroxy-4-substituted pyridine derivatives.

benzene in a round bottom flask was refluxed for 4 h. Allowed to cool, then filtered the products and recrystallized from benzene.

*3-Hydroxy-2,6-dimethylpyridine-4-carbonitrile(**2**).* White powder; yield 0.48 g (65%); mp 176–177°C; IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3550 (OH), 2986 (CH-aliph.), 2218 (CN), 1590 (C=N), 1538 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.53 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.59 (bs, 1H, OH), 7.86 (s, 1H, CH=); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 14.0, 21.8, 108.1, 117.3, 123.8, 150.8, 153.7; MS: m/z = 148 (M^+). Calcd for $C_8H_8N_2O$ (148.16): C, 64.85; H, 5.44, N, 18.91%. Found: C, 64.79; H, 5.48; N, 18.86%.

*3-Hydroxy-2,6-dimethylpyridine-4-carboxylaldehyde (**3**).* White powder; yield 0.45 g (60%); mp >300°C; IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3545 (OH), 2980 (CH-aliph.), 1670 (CO), 1584 (C=N), 1532 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.50 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.54 (bs, 1H, OH), 7.82 (s, 1H, CH=), 9.43 (s, 1H, CHO); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 11.4, 19.4, 123.1, 129.3, 149.3, 150.2, 151.4, 195.7; MS: m/z = 151 (M^+). Calcd for $C_8H_9NO_2$ (151.16): C, 63.56; H, 6.00, N, 9.27%. Found: C, 63.52; H, 5.98; N, 9.26%.

*3-Hydroxy-2,6-dimethylpyridine-4-carboxylic acid (**4**).* White crystals; yield 0.7 g (84%); mp 294–295°C (lit [22], 290–291°C); IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3553 (OH), 2959 (CH-aliph.), 1665 (CO), 1580 (C=N), 1525 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 2.46 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.40 (bs, 1H, OH), 7.67 (s, 1H, CH=); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 14.7, 18.4, 123.3, 143.3, 149.9, 154.3, 165.9, 197.3; MS: m/z = 167 (M^+). Calcd for $C_8H_9NO_3$ (167.16): C, 57.48; H, 5.43, N, 8.38%. Found: C, 57.39; H, 5.41; N, 8.32%.

*Methyl 3-hydroxy-2,6-dimethylpyridine-4-carboxylate (**5**).* White crystals; yield 0.8 g (90%); mp 90–91°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3542 (OH), 2981 (CH-aliph.), 1660 (CO), 1585 (C=N), 1530 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.60 (bs, 1H, OH), 2.49 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 7.52 (s, 1H, CH=); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.8, 23.6, 52.5, 123.8, 125.4, 148.3, 149.1, 150.0, 164.6; MS: m/z = 181 (M^+). Calcd for $C_9H_{11}NO_3$ (181.19): C, 59.66; H, 6.12, N, 7.73%. Found: C, 59.69; H, 6.11; N, 7.68%.

*tert-Butyl 5-Hydroxy-2,6-dimethylpyridine-3-carboxylate (**6**).* White crystals; yield 0.94 g (84%); mp 205–206°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3340 (OH), 2982 (CH-aliph.), 1716 (CO), 1582 (C=N), 1528 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.55 (s, 9H, $3CH_3$), 1.61 (bs, 1H, OH), 2.49 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 7.52 (s, 1H, CH=); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.8, 23.6, 28.2 (3C), 81.9, 123.9, 125.4, 148.3, 149.1, 150.1, 165.9; MS: m/z = 223 (M^+). Calcd for $C_{12}H_{17}NO_3$ (223.27): C, 64.55; H, 7.67, N, 6.27%. Found: C, 64.48; H, 7.61; N, 6.25%.

*3-Hydroxy-2,5,6-trimethylpyridine-4-carboxylaldehyde (**7**).* White powder; yield 0.7 g (65%); mp 75–76°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3457 (OH), 2975 (CH-aliph.), 1673 (CO), 1592 (C=N), 1538 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.21 (bs, 1H, OH), 9.27 (s, 1H, CHO); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 14.9, 15.2, 17.9, 131.1, 143.7, 149.3, 155.2, 168.9, 190.1; MS: m/z = 165 (M^+). Calcd for $C_9H_{11}NO_2$ (165.19): C, 65.44; H, 6.71, N, 8.48%. Found: C, 65.43; H, 6.64; N, 8.42%.

*Dimethyl 5-hydroxy-2,6-dimethylpyridine-3,4-dicarboxylate (**8**).* White crystals; yield 0.84 g (70%); mp 113–114°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3543 (OH), 2987 (CH-aliph.), 1670 (CO), 1724 (CO), 1583 (C=N), 1535 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.12 (bs, 1H, OH), 3.62 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 7.42 (s, 1H, CH=); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 15.1, 18.7, 52.7, 52.9, 129.3, 143.2, 149.5, 155.1, 167.6, 170.2, 172.1; MS: m/z = 239 (M^+). Calcd for $C_{11}H_{13}NO_5$ (239.22): C, 55.23; H, 5.48, N, 5.86%. Found: C, 55.19; H, 5.46; N, 5.84%.

*4,5-Bis(hydroxymethyl)-2,6-dimethylpyridine-3-ol (**9**).* White crystals; yield 0.6 g (65%); mp 105–106°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3540 (OH), 2976 (CH-aliph.), 1585 (C=N), 1530 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.49 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.40 (bs, 1H, OH), 4.67 (s, 4H, $2CH_2OH$); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 11.7, 15.4, 52.7, 56.1, 131.2, 134.9, 145.7, 149.9, 151.4; MS: m/z = 183 (M^+). Calcd for $C_9H_{13}NO_3$ (183.20): C, 59.00; H, 7.18, N, 7.65%. Found: C, 59.11; H, 7.13; N, 7.69%.

*7-Hydroxy-4,6-dimethylfuro[3,4-c]pyridine-1,3-dione (**10**).* Brown powder; yield 0.89 g (92%); mp 235–236°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3453 (OH), 2976 (CH-aliph.), 1868 (CO), 1792 (CO), 1596 (C=N), 1534 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 2.44 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.43 (bs, 1H, OH); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 12.4, 14.3, 123.9, 127.9, 149.8, 151.3, 153.6, 162.1, 162.5; MS: m/z = 193 (M^+). Calcd for $C_9H_7NO_4$ (193.16): C, 55.96; H, 3.65, N, 7.25%. Found: C, 55.60; H, 3.63; N, 7.23%.

*7-Hydroxy-2,4,6-trimethyl-2H-pyrrolo[3,4-c]pyridine-1,3-dione (**11**).* Orange crystals; yield 0.93 g (90%); mp 105–106°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3553 (OH), 2960 (CH-aliph.), 1750 (CO), 1720 (CO), 1664 (C=N), 1538 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.57 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.61 (bs, 1H, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 19.2, 20.1, 23.9, 119.6, 128.3, 145.4, 147.1, 155.7, 167.9, 169.2; MS: m/z = 206 (M^+). Calcd for $C_{10}H_{10}N_2O_3$ (206.20): C, 58.25; H, 4.89, N, 13.59%. Found: C, 58.21; H, 4.86; N, 13.64%.

*2-(7-Hydroxy-4,6-dimethyl-1,3-dioxo-1H-pyrrolo-[3,4-c]pyridin-2(3H)-yl) Acetic Acid (**12**).* Yellowish white crystals; yield 1.15 g (92%); mp 252–253°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3555 (OH), 2973 (CH-aliph.), 1750 (CO), 1702 (CO), 1695 (CO), 1610 (C=N), 1538 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 2.49 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.42 (bs, 1H, OH), 4.24 (s, 2H, CH_2); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 19.1, 19.6, 38.3, 119.6, 119.8, 144.9, 156.8, 165.1, 166.7, 168.3; MS: m/z = 250 (M^+). Calcd for $C_{11}H_{10}N_2O_5$ (250.21): C, 52.80; H, 4.03, N, 11.20%. Found: C, 52.78; H, 4.01; N, 11.17%.

*(S)-2-(7-Hydroxy-4,6-dimethyl-1,3-dioxo-1H-pyrrolo[3,4-c]pyridin-2(3H)-yl) Propanoic Acid (**13**).* White crystals; yield 0.92 g (70%); mp = 127–128°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3545 (OH), 2965 (CH-aliph.), 1723 (CO), 1610 (C=N), 1540 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 1.43 (d, J = 7.5 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.42 (bs, 1H, OH), 4.67 (q, J = 7.5 Hz, 1H, CH); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 13.6, 14.2, 18.1, 49.4, 126.5, 131.6, 146.4, 149.8, 154.1, 165.9, 166.1; MS: m/z = 264 (M^+). Calcd for $C_{12}H_{12}N_2O_5$ (264.23): C, 54.55; H, 4.58, N, 10.60%. Found: C, 54.52; H, 4.52; N, 10.62%.

*4-Hydroxy-1,3-dimethylisoquinoline-5,8-dione (**14**).* Violet crystals; yield 0.97 g (96%); mp >300°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3560 (OH), 2986 (CH-aliph.), 1735 (CO), 1600 (C=N), 1545 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 2.47 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.48 (bs, 1H, OH), 7.12 (d, J = 9.9 Hz, 1H, CH=) 7.15 (d, J = 9.9 Hz, 1H, CH=); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 14.5, 18.2, 128.1, 129.6, 141.3, 141.6, 149.9, 153.8, 154.3, 187.3, 187.9; MS: m/z = 203 (M^+). Calcd for $C_{11}H_9NO_3$ (203.19): C, 65.02; H, 4.46, N, 6.89%. Found: C, 65.17; H, 4.37; N, 6.74%.

*4-Hydroxy-1,3-dimethylbenzo[g]isoquinoline-5,10-dione (**15**).* Violet crystals; yield 1.21 g (96%); mp >300°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3565 (OH), 2974 (CH-aliph.), 1738 (CO), 1595 (C=N), 1528 (C=C);

TABLE 1 Crystal Structure Data for Compounds **5, 6**, and **17**

Compound	**5**	**6**	**17**
Empirical formula	$C_9H_{11}NO_3$	$C_{12}H_{17}NO_3$	$C_{16}H_{12}N_2O_5$
Formula mass	181.19	223.27	312.28
Color	Colorless	Colorless	Green
Temperature (K)	293 (2)	293 (2)	293 (2)
Wavelength (Å)	0.71073	0.71073	0.71073
Size (mm)	0.25 × 0.15 × 0.15	0.15 × 0.15 × 0.10	0.30 × 0.30 × 0.20
a (Å)	4.831 (10)	9.329 (1)	7.3706 (3)
b (Å)	11.381 (10)	25.068 (1)	21.1124 (13)
c (Å)	8.634 (10)	11.165 (1)	11.3856 (5)
α (°)	90	90	90 (1)
β (°)	105.17	90	127.521 (3)
γ (°)	90	90	90 (1)
V (Å^3)	458.17 (12)	2611.0 (4)	1405.21 (12)
Z	2	8	4
$d_{calcd.}$ (g/cm^3)	1.270	1.136	1.476
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P21/m$	$Pccn$	$P21/c$
No. refl. meas.	1022	8532	11044
No. uni. Refl.	1022	2613	3063
No. obs. Refl.[a]	815	1112	1570
R	0.0373	0.0548	0.0382
R_w	0.0746	0.1350	0.1062
Largest diff. Peak/hole (e/Å^{-3})	0.123/−0.111	0.170/−0.168	0.262/−0.180

[a]For $I > 2\sigma(I)$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 2.49 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.44 (bs, 1H, OH), 7.64–8.00 (m, 4H, Ar.H); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 14.2, 18.8, 129.7, 129.9, 130.2, 132.2, 132.9, 134.8, 135.2, 148.8, 150.9, 154.3, 186.7, 187.3; MS: m/z = 253 (M^+). Calcd for $C_{15}H_{11}NO_3$ (253.25): C, 71.14; H, 4.38, N, 5.53%. Found: C, 71.08; H, 4.32; N, 5.47%.

*7-Hydroxy-4,6-dimethyl-2-o-tolyl-2H-pyrrolo[3,4-c]pyridine-1,3-dione (***16***).* Yellow crystals; yield 1.19 g (85%); mp = 190–191°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3553 (OH), 2964 (CH-aliph.), 1708 (CO), 1584 (C=N), 1527 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.19 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.49 (bs, 1H, OH), 7.14 (d, J = 7.5 Hz, 1H, Ar.H), 7.31–7.37 (m, 3H, Ar.H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.0, 19.2, 20.2, 126.9, 128.6, 129.7, 131.3, 136.4, 145.9, 147.8, 156.0, 168.3, 181.3; MS: m/z = 282 (M^+). Calcd for $C_{16}H_{14}N_2O_3$ (282.16): C, 68.07; H, 5.00, N, 9.92%. Found: C, 67.95; H, 5.01; N, 9.86%.

*2-(7-Hydroxy-4,6-dimethyl-1,3-dioxo-1H-pyrrolo-[3,4-c]pyridin-2(3H)-yl)benzoic Acid (***17***).* Green crystals; yield 1.36 g (87%); mp 255–256°C; IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3543 (OH), 2974 (CH-aliph.), 1716 (CO), 1695 (CO), 1600 (C=N), 1535 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_{ppm} = 2.45 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.34 (bs, 1H, OH), 7.41–7.44 (dd, J = 7.8, 3.12 Hz, 1H, Ar.H), 7.52–7.57 (ddd, J = 15.3, 7.5, 3.12 Hz, 1H, Ar.H), 7.67–7.72 (ddd, J = 15.3, 3.12, 1.92 Hz, 1H, Ar.H), 7.95–7.98 (dd, J = 7.8, 1.47 Hz, 1H, Ar.H), 11.01 (s, 1H, CO_2H); ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ_{ppm} = 19.7, 20.1, 120.4, 120.6, 129.3, 129.4, 130.7, 131.1, 131.4, 133.1, 145.1, 145.5, 157.1, 165.6, 166.1, 167.2; MS: m/z = 312 (M^+). Calcd for $C_{16}H_{12}N_2O_5$ (312.28): C, 61.54; H, 3.87, N, 8.97%. Found: C, 61.48; H, 3.79; N, 8.93%.

X-ray Crystallographic Studies

All data sets were collected with an Enraf Nonius CACD-4 diffractometer. Hydrogen atoms were calculated and refined as riding atoms. Crystal structure data and details are listed in Table 1.

ACKNOWLEDGMENTS

We wish to thank Prof. A. G. Griesbeck, Institute of Organic Chemistry,University of Cologne, Germany, for advice and for helpful discussions. We are also indebted to Dr. J. Lex and Dr. J. Neudörf, university of Cologne, Germany, for X-ray measurements.

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