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CATHYLATION OF 4,6-DIMETHYL-2-OXOPYRIDINE-3-CARBONITRILE DERIVATIVES LEADING TO THE SYNTHESIS OF FURO[2,3-*b*;4,5-*b'*]DIPYRIDINES AND NOVEL TRICYCLIC FURO[2,3,4-*ij*][2,7]-NAPHTHYRIDINE

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Abstract - Cathylation of ethyl 2-(3-cyano-4,6-dimethylpyridine-2-yloxy)acetate afforded a trace amount of new tricyclic furo[*2,3,4-ij*][2,7]naphthyridine derivative. An attempt was made for an alternate method for the synthesis this new tricyclic ring system. Treatment of 4,6-dimethyl-2-oxopyridine-3-carbonitrile (**1**) with various α-halocarbonyl compounds (such as chloropropanone or substituted 2-bromoacetophenones) gave a mixture of *N*- and *O*-alkylated compounds, which were readily converted into indolizines and 2-acetyl-3-amino- or 3-amino-2-benzoylfuro[2,3-*b*]pyridines. The 3-aminofuro[2,3-*b*]pyridine derivatives were further converted into furo[2,3-*b*;4,5-*b'*]dipyridines, but not the expected tricyclic furonaphthyridines, *via N,O*-acetylation and cyclization.

INTRODUCTION

Methylpyridin-2-ones or their 3-cyano derivatives show several possibilities for the construction of other heterocyclic ring systems. For example, Adams *et al*.[1] reported the treatment of 1-benzyl-6-methyl-2-oxopyridine with ethyl oxalate gave ethyl 3-(1-benzyl-2-oxopyridin-6-yl)pyruvate, which was then converted into ethyl 2-(2-oxopyridin-6-yl)acetate *via* hydrolysis, alkaline peroxide oxidation, and esterification. Condensation of ethyl 2-(2-oxopyridin-6-yl)acetate with diethyl ethoxymethylenemalonate formed diethyl-6-hydroxy-4-quinolizone-1,3-dicarboxylate. Wani *et al*.[2] also reported that 4-methyl-2-oxopyridine-3-carbonitrile derivative was converted into the corresponding 4-ethoxycarbonylmethyl

derivatives *via* direct cathylation (carboethoxylation, diethyl carbonate/KH) at C4-Me function. The product was an important intermediate for the synthesis of camptothecin, a topoisomerase I mediated anticancer agent. In addition, Gewald *et al*.[3] reported that the reaction of 2-oxopyridine-3-carbonitrile with α-halocarbonyl compounds yielded a mixture of 1-alkyl-2-oxopyridine-3-carbonitrile and 2-alkoxy-pyridines-3-carbonitrile, and the latter compound can be cyclized in the presence of sodium ethoxide to form 3-aminofuro[2,3-*b*]pyridines. In a similar manner, a mixture of 2-alkoxy-2-oxopyridine-3-carbonitrile and 1-alkyl-2-oxopyridine-3-carbonitrile (**2** and **4**, respectively) was obtained from 4,6-dimethyl-2-oxopyridine-3-carbonitrile (**1**) and was cyclized to yield indolizines (**3**) and 3-aminofuropyridines (**5**), respectively. Reaction of *N*-acetyl derivatives of 3-aminofuropyridine (**5**) with ammonium acetate readily produced the tricyclic pyridofuropyrimidines (**6**).

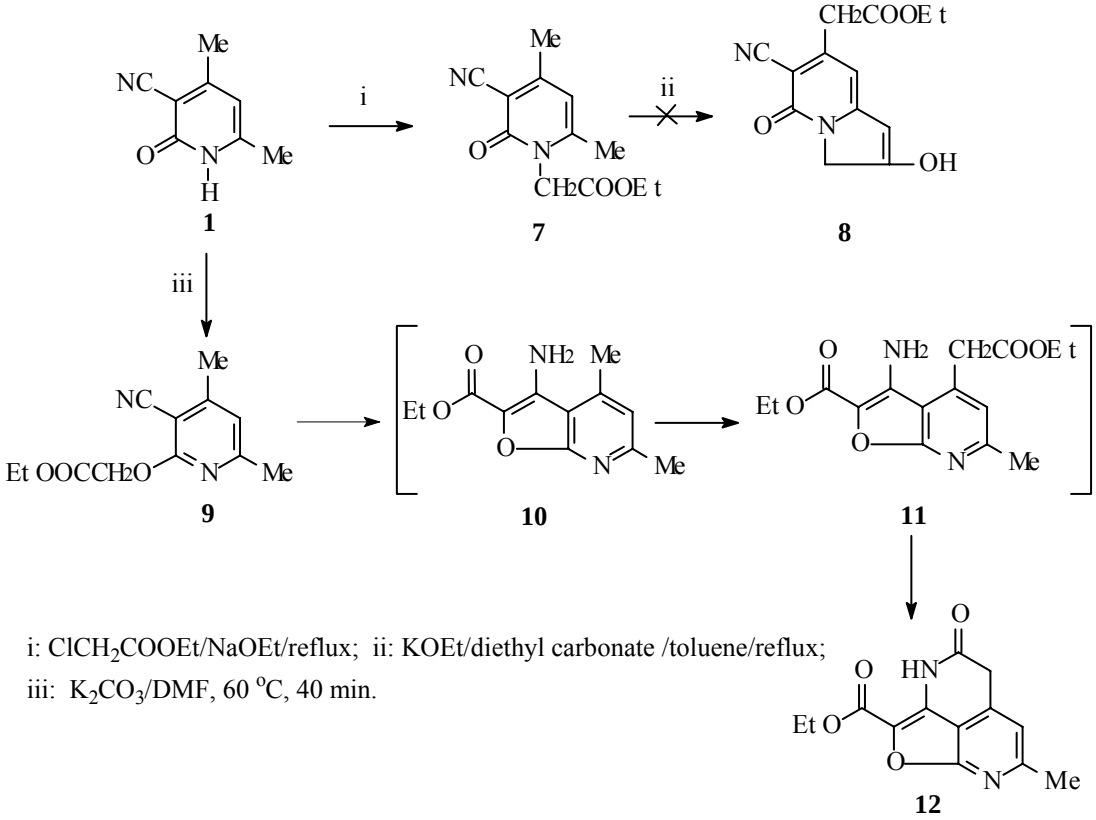
During the course of our studies on the synthesis of biologically active heterocyclic compounds, we failed to convert the known 3-cyano-4,6-dimethyl-1-ethoxycarbonyl-2-oxopyridine (**7**) into bicyclic indolizine (**8**) *via* cathylation at C4-Me groups and simultaneous ring closure by attacking the generated carbanion at C6-Me to the ester function. We, therefore, studied the cathylation of the methyl groups of **1**[4] to construct heterocyclic ring. We found that cathylation of the known ethyl 2-(3-cyano-4,6-dimethylpyridin-2-yloxy)acetate (**9**, Scheme 1)[3] gave a trace amount of new tricyclic furo[2,3,4-*ij*][2,7]naphthyridin-4-one (**12**). However, the tricyclic product was not isolated by us consistently. To explore the synthesis of the tricyclic ring system, an attempt was made for an alternate method for the synthesis of this new tricyclic system by using the known bicyclic 3-aminofuropyridine (**5**)[3] as a starting material. However, we obtained furodipyridines from **5**. In this paper, we describe the cathylation of **9** that leads to the synthesis of furodipyridines and novel tricyclic furonaphthyridines.

CHEMISTRY

Cathylation of ethyl 2-(3-cyano-4,6-dimethylpyridin-2-yloxy)acetate (9) The known ethyl 2-(3-cyano-4,6-dimethylpyridin-2-yloxy)acetate (**9**) was prepared by the reaction of **1** with ethyl bromoacetate.[3] Treatment of compound (**9**) with an excess of diethyl carbonate in dry toluene in the presence of KOEt afforded trace amount of new tricyclic furo[2,3,4-*ij*][2,7]naphthyridin-4-one (**12**). However, we were not able to isolate the tricyclic compound (**12**) consistently, probably due to its instability under the applied reaction conditions. The ^{1}H-NMR spectrum of **12** showed one triplet (3H) at δ 1.32 assigned for Me, one singlet at δ 2.58 for C7-Me, one singlet (2H) at δ 4.06 for C5-CH_2, one quartet (2H) at δ 4.34 for CH_2, and one singlet (1H) at δ 7.13 for C6-H. The C5-CH_2 group is acidic as shown by D_2O exchange experiment. A plausible reaction mechanism of the formation of **12** is shown in Scheme 2. A carbanion was generated at the methylene function adjacent to the ester group. This

carbanion attacked the C3-cyano function to yield the known bicyclic 3-aminofuro[2,3-*b*]pyridine (**10**) intermediate.[3] Cathylation of **10** occurred simultaneously at C4-Me to form intermediate (**11**), which was readily converted to produce the tricyclic compound (**12**) by cyclization between the amino group and the C4-ester group.

Scheme 1



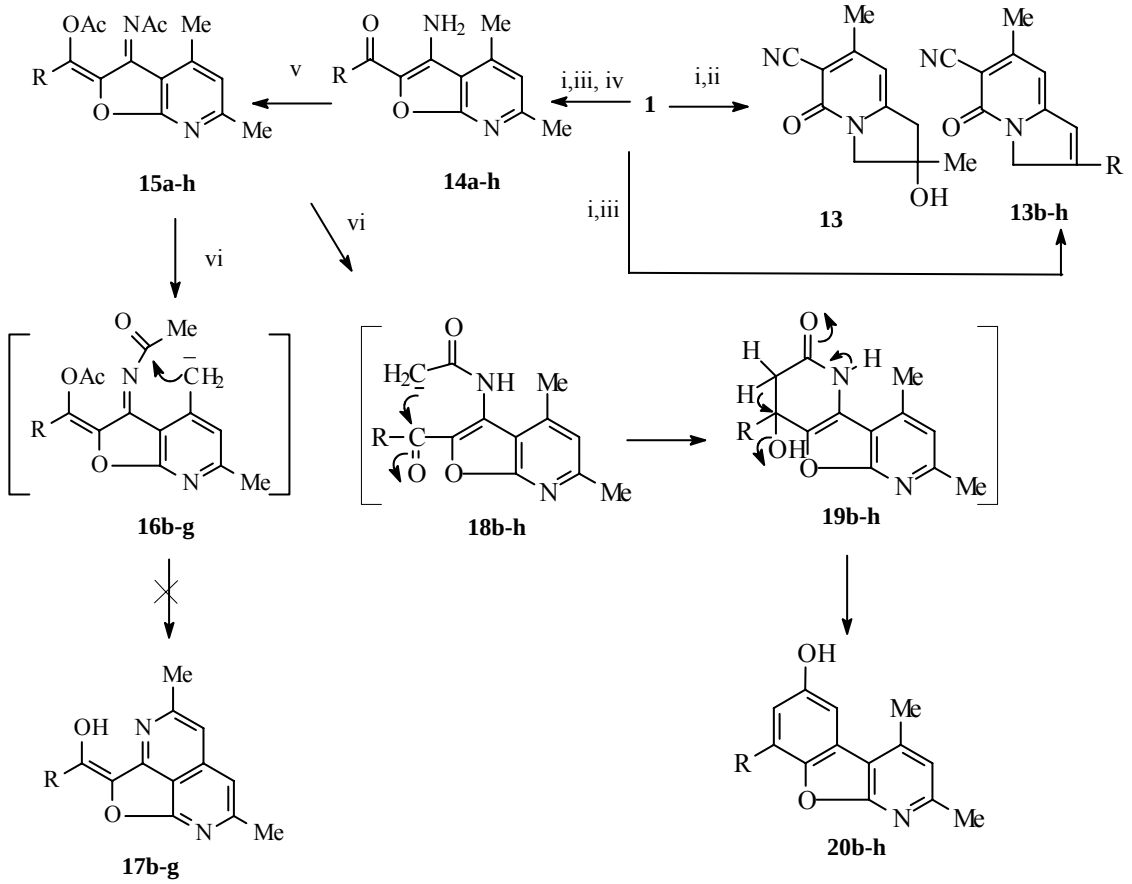
i: $ClCH_2COOEt/NaOEt/reflux$; ii: KOEt/diethyl carbonate /toluene/reflux;
iii: K_2CO_3/DMF, 60 ^oC, 40 min.

Synthesis of tricyclic furo[2,3-*b*;4,5-*b'*]dipyridine (20b-g and 24) To explore the synthetic chemistry for the preparation of new tricyclic ring furonaphthyridine system, an attempt was made for alternative synthetic method. The plausible reaction mechanism of formation of new tricyclic compound (**12**) (Scheme 1) suggests that this tricyclic ring system may also be prepared from the 3-aminofuropyridine derivatives such as **5**. One can synthesize *N*-acetyl derivative (**15**), and a carbanion may be generated from its C4-Me. The carbanion may then attack the *N*-acetyl C=O group to furnish new tricyclic compound as shown in Scheme 2.

Following the method developed by Gewald *et al.*,[3] the potassium salt of **1** reacted with various α-halocarbonyl compounds such as chloropropanone or 2-bromoacetophenones to afford a mixture of *N*- and *O*-alkylated products which were not separated but directly treated with ethanolic sodium ethoxide (80 ^oC/5 min) to give indolizines (**13** and **13b-h**) and 3-aminofuro[2,3-*b*]pyridines (**14a-h**), respectively (Scheme 2). The 3-aminofuro[2,3-*b*]pyridines (**14a-h**) were then treated with acetic anhydride in pyridine to afford *N,O*-diacetyl derivatives (**15a-h**), which cannot be purified by column chromatography,

since the enol acetate is quite unstable even in weak acidic medium such as silica gel. After purification by recrystallization from EtOH, compounds (**15a-h**) were further treated with KH in refluxing toluene. All compounds, except 4-nitrophenyl derivative (**15h**), were converted smoothly into the tricyclic 2-hydroxyfuro[2,3-*b*;4,5-*b'*]dipyridine derivatives (**20b-g**) in moderate to good yields, but not to furonaphthyridines (**17b-g**). Compound (**15h**) is extremely unstable in alkaline medium and cannot be converted into the corresponding tricyclic compound under various conditions. Formation of the tricyclic furondipyridines from **15b-g** suggests that a carbanion is generated from the Me function of the *N*-acetyl group. The carbanion then attacks the carbonyl function to furnish the intermediates (**19b-g**), which are further converted to the tricyclic furodipyridines (**20b-g**) (Scheme 2). Unlike phenyl substituted derivatives (**15b-g**), compound (**15a**) also gave the 4-hydroxyfuro[2,3-*b*;4,5-*b'*]dipyridine derivative (**24**) (Scheme 3). Apparently, the *O*-deacetylation is occurred under the reaction conditions with the formation of ketone (**22**) from **15a**. A carbanion is generated from the keto-methyl carbon, which further attacks the *N*-acetyl group to give the furodipyridine (**24**).

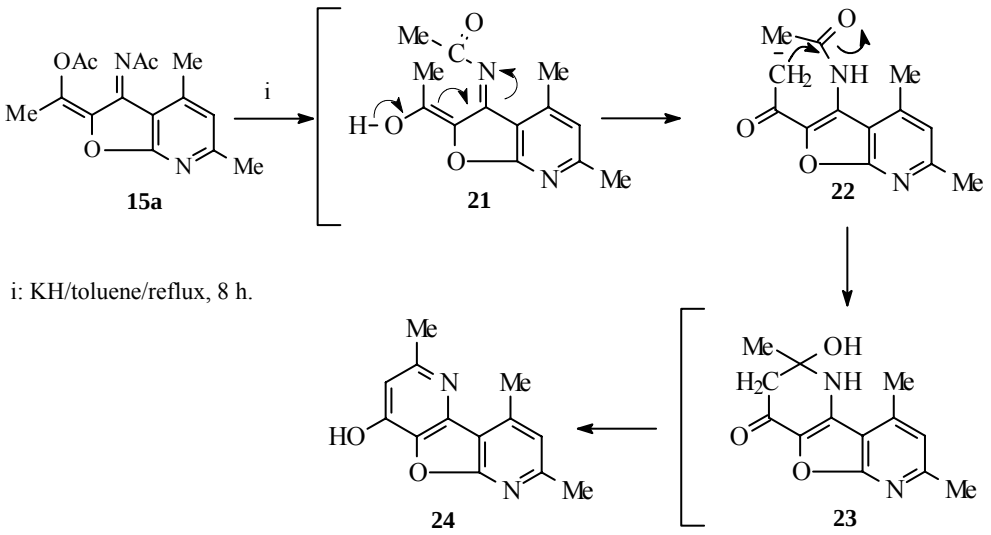
Scheme 2



a: R = Me; b: R = C_6H_5; c: R = C_6H_4-(4-F); d: R = C_6H_4-(4-Cl); e: R = C_6H_4-(4-Br); f: R = C_6H_4-(4-Me); g: R = C_6H_4-(4-OMe); h: R = C_6H_4-(4-NO_2)

i: KOH/EtOH; ii: $ClCH_2COOEt$/DMF/50 ^oC, 4 h; iii: $RCOCH_2Br$/DMF, 50 ^oC, 4 h; iv: NaOEt/reflux, 3 min; v: Ac_2O/Py/100 ^oC, 8 h; vi: KH/toluene/reflux, 8 h.

Scheme 3



In comparison to the ^{1}H-NMR spectrum of 2-hydroxy substituted furodipyridines (**20b-g**) and 4-hydroxy substituted derivative (**24**), both Me-7 and Me-9 coupled with H-8 in HMBC ^{3}J measurement (Figure 1). In the series of 2-hydroxy substituted derivatives, the H-3 has no ^{3}J coupling, while the 4-hydroxy substituted derivative has one Me-H ^{3}J coupling.

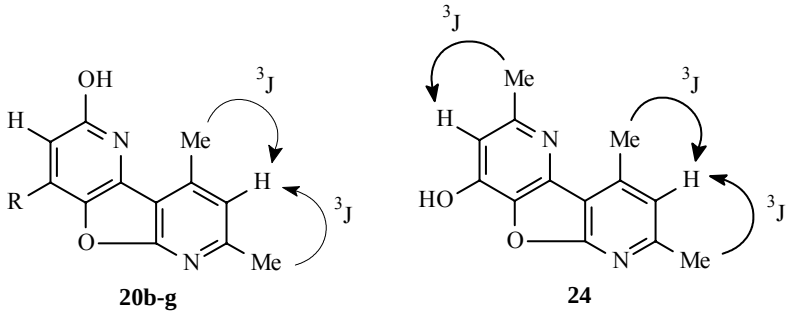


Figure 1

DISCUSSION

Furo[2,3-*b*]pyridine derivatives have been synthesized by several synthetic routes.[3,5-10] The synthesis of furo[2,3-*b*]pyridine reported by Robertson and Watt[5] is based upon a coumarilic acid-type rearrangement of 3,6-dibromo-7-hydroxy-5-methylpyrano[2,3-*b*]-2-oxopyridine. Another method for the preparation of the bicyclic ring system described by Reisch[6] involved the cyclization of an acetylenic pyridine. Snyder *et al.*[7]obtained furopyridines from the reaction of 2-aminofurans with trifluoroacetoacetate or sodium nitromalonaldehyde. In addition, furo[2,3-*b*]pyridines were synthesized by the condensation of ethyl 2-chloronicotinate with sodium ethoxycarbonylmethoxide followed by ring closure to form the second furan ring.[8,9] In the present paper, we adapted the Gewald's method and prepared a series of C2-substituted 3-aminofuro[2,3-*b*]pyridines as major product along with indolizines as by-product by the

reaction of **1** with various α-halocarbonyl derivatives. The 3-aminofuro[2,3-*b*]pyridines were previously converted to tricyclic pyridofuropyrimidines (**6**).[3] At present, we transformed 3-aminofuro[2,3-*b*]pyridines to furo[2,3-*b*;4,5-*b'*]dipyridines (**20b-g** and **24**) from **15a-g**.

In summary, the acidic properties of the methyl groups in 4,6-dimethyl-2-oxopyridine-3-carbonitrile (**1**) show some possibilities for the construction of various heterocyclic compounds. Cathylation of the methyl groups of **9** giving the tricyclic compound **12** led us to develop a synthetic route to prepare tricyclic furodipyridine system. The tricyclic compounds (**20b-g** and **24**) were subjected for *in vitro* antitumor evaluation. Of these compounds, only compound (**20g**) was revealed to have moderate inhibitory effect against human lung cancer H23 cell growth in culture.

EXPERIMENTAL

Melting points were determined on a Fargo melting capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70-230 mesh, ASTM, Merck). Thin layer chromatography was done on silica gel F254 plate (Merck) with short-wavelength UV light for visualization. IR spectra were determined on Back Scientific Inc. Model 500 spectrophotometer. ^{1}H-NMR spectra were recorded on Brucker-400 spectrometer at 400 MHz with TMS as an internal standard. Values reported for coupling constants are first order. Elemental analyses were performed on a Heraeus CHN-O Rapid instrument.

Synthesis of indolizines (13 and 13b-h) and 3-aminofuro[2,3-*b*]pyridines (14a-h)

The following indolizines and 3-aminofuro[2,3-*b*]pyridine were prepared by Gewald's method.[3] A mixture of potassium salt of **1** (4.5 g, 24.2 mmol)[4] and chloropropanone (2.24 g, 24.2 mmol) in dry DMF (50 mL) was stirred at 50 ^{o}C for 4 h. Ice-water (100 mL) was added into the mixture and the resulting precipitates were collected by filtration, washed with water and dried. The solid was treated with ethanolic sodium ethoxide freshly prepared by dissolving Na (0.56 g, 24.2 mmol) in dry EtOH (40 mL) in an oil-bath preheated to 80 ^{o}C for 3 min. After cooling, the mixture was diluted with ice-water (50 mL), and the precipitates were collected by filtration, washed with EtOH, and recrystallized from EtOH to give (**14a)**, 360 mg (25%); mp 230-231 ^{o}C; IR (KBr): cm^{-1} 1610; ^{1}H-NMR (DMSO- d_6): δ 2.37 (3H, s, COMe), 2.50 and 2.64 (each 3H, s, 2 x Me), 6.67 (2H, s, exchangeable, NH_2), 7.01 (1H, s, ArH). *Anal*. Calcd for $C_{11}H_{12}N_2O_2 \cdot 1/16H_2O$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.77; H, 5.94; N, 13.44.

The filtrate was acidified with acetic acid and the resulting precipitates were collected by filtration and washed with EtOH. The solid cake was recrystallized from EtOH to give the known indolizine (**13)**, 250 mg (17%); mp 220-221 ^{o}C; IR (KBr): cm^{-1}1685, 2210; ^{1}H -NMR (DMSO- d_6): δ 1.41 (3H, s, Me), 2.35 (3H, s, Me), 3.08 (2H, dd, J = 17.2 and 19.2 Hz, CH_2), 3.90 (2H, dd, J = 12.7 and 12.8 Hz, CH_2), 5.33

(1H, s, OH), 6.36 (1H, s, ArH). *Anal*. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.77; H, 5.94; N, 13.44.

In a similar manner to that for the synthesis of **13** and **14a**, the following indolizines (**13b-h**) and 3-aminofuropyridines (**14b-h**) were prepared.

7-Methyl-5-oxo-2-phenyl-3,5-dihydroindolizine-6-carbonitrile (13b) and 3-amino-2-benzoyl-4,6-dimethylfuro[2,3-*b*]pyridine (14b)

Compounds (**13b**) and (**14b**) were prepared from the K-salt of **1** (4.5 g, 24.2 mmol) and bromoacetophenone (4.11 g, 26.6 mmol). **13b**: 30 mg (2%); mp 288-289 ^oC (decomp); IR (KBr): cm^{-1} 1652, 2205; ^1H-NMR (DMSO-d_6): δ 2.44 (3H, s, Me), 5.26 (2H, s, CH_2), 6.61 and 7.41 (each 1H, s, ArH), 7.49 (3H, m, ArH), 7.82 (2H, m, ArH). *Anal*. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.32; H, 4.89; N, 11.00. **14b**: 1.34 g (88%); mp 157-158 ^oC; IR (KBr): cm^{-1} 1652 ^1H-NMR (DMSO-d_6): δ 2.51 and 2.70 (each 3H, s, Me), 7.06 (1H, s, ArH), 7.26 (2H, s, exchangeable, NH_2), 7.59 (3H, m, ArH) and 8.07 (2H, m, ArH). *Anal*. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.97; H, 5.32; N, 10.42.

2-(4-Fluorophenyl)-7-methyl-5-oxo-3,5-dihydroindolizine-6-carbonitrile (13c) and 3-amino-2(4-fluorobenzoyl)-4,6-dimethylfuro[2,3-*b*]pyridine (14c)

Compounds (**13c**) and (**14c**) were prepared from the K-salt of **1** (4.66 g, 25 mmol) and 2-bromo-4'-fluoroacetophenone (5.43 g, 25 mmol). **13c**: 0.49 g (36%); mp 266-268 ^oC; IR (KBr): cm^{-1} 1650, 2208; ^1H-NMR (DMSO-d_6): δ 2.43 (3H, s, Me), 5.25 (2H, s, CH_2), 6.60 and 7.37 (each 1H, s, ArH), 7.35 (2H, t, J = 8.2 Hz, ArH), 7.90 (2H, dd, $J_{H,F}$ = 6.2 Hz, $J_{H,H}$ = 8.2 Hz, ArH). *Anal*. Calcd for $C_{16}H_{11}N_2OF{\cdot}3H_2O$: C, 70.97; H, 4.09; N, 10.35. Found: C, 70.87; H, 4.24; N, 10.00. **14c**: 0.66 g (45 %); mp 222-223 ^oC; IR (KBr): cm^{-1} 1650; ^1H-NMR (DMSO-d_6): δ 2.52 and 2.70 (each 3H, s, Me), 7.07 (1H, s, ArH), 7.31 (2H, s, exchangeable, NH_2), 7.40 (2H, t, $J_{H,H}$= 8.3 Hz, ArH), 8.17 (2H, dd, $J_{H,F}$ = 6.1, Hz, $J_{H,H}$ = 8.3 Hz, ArH). *Anal*. Calcd for $C_{16}H_{13}N_2O_2F$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.59; H, 4.63; N, 9.80.

2-(4-Chlorophenyl)-7-methyl-5-oxo-3,5-dihydroindolizine-6-carbonitrile (13d) and 3-amino-2-(4-chlorobenzoyl)-4,6-dimethylfuro[2,3-*b*]pyridine (14d)

Compounds (**13d)** and (**14d**) were prepared from the K-salt of **1** (5.59 g, 30 mmol) and 2-bromo-4'-chloroacetophenone (7.39 g, 31 mmol). **13d**: 0.51 g (36%); mp 260-261 ^oC (decomp); IR (KBr): cm^{-1} 1648, 2211; ^1H-NMR (DMSO-d_6): δ 2.44 (3H, s, Me), 5.24 (2H, s, NCH_2), 6.61 and 7.44 (each 1H, s, ArH), 7.57 and 7.85 (each 2H, d, J = 8.6 Hz, ArH). *Anal*. Calcd for $C_{16}H_{11}N_2OCl$: C, 67.97; H, 3.92; N, 9.90. Found: C, 67.72; H, 3.95; N, 9.79. **14d**: 0,55 g (36%); mp 224-225 ^oC; IR (KBr): cm^{-1} 1650; ^1H-NMR (DMSO-d_6): δ 2.52 and 2.70 (each 3H, s, Me), 7.07 (1H, s, ArH), 7.31 (2H, s, exchangeable, NH_2),

7.65 and 8.10 (each 2H, d, J = 8.5 Hz, ArH). *Ana*l. Calcd for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; H, 4.36; Cl, N, 9.32. Found: C, 63.70; H, 4.37; N, 9.23.

2-(4-Bromophenyl)-7-methyl-5-oxo-3,5-dihydroindolizine-6-carbonitrile (13e) and 3-amino-2-(4-bromobenzoyl)-4,6-dimethylfuro[2,3-*b*]pyridine (14e)

Compounds (**13e**) and (**14e**) were prepared from the K-salt of **1** (5.59 g, 30 mmol) and 2-bromo-4'-chloroacetophenone (8.79 g, 31 mmol). **13e**: 0.45 g (32 %); mp 260-261 ^oC (decomp); IR (KBr): cm^{-1} 1651, 2209; ^1H-NMR (DMSO-d_6): δ 2.50 (3H, s, Me), 5.24 (2H, s, NCH_2), 6.61 and 7.45 (each 1H, s, ArH), 7.71 and 7.78 (each 2H, d, J = 8.2 Hz, ArH). *Anal*. Calcd for $C_{16}H_{11}N_2OBr$: C, 58.73; H, 3.39; N, 8.56. Found: C, 58.62; H, 3.42; N, 8.42. **14e**: 0.54 g (36%); mp. 223-224 ^oC. IR (KBr): cm^{-1} 1652; ^1H-NMR (DMSO-d_6): δ 2.50 and 2.69 (each 3H, s, Me), 7.06 (1H, s, ArH), 7.31 (2H, s, exchangeable, NH_2), 7.79 and 8.03 (each 2H, d, J = 8.4 Hz, ArH). *Anal*. Calcd for $C_{16}H_{13}N_2O_2Br$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.60; H, 3.71; N, 8.01.

7-Methyl-2-(4-methylphenyl)-5-oxo-3,5-dihydroindolizine-6-carbonitrile (13f) and 3-amino-2-(4-methylbenzoyl)-4,6-dimethylfuro[2,3-*b*]pyridine (14f)

Compounds (**13f**) and (**14f**) were prepared from the K-salt of **1** (4.02 g, 21.6 mmol) and 2-bromo-4'-methylacetophenone (4.60 g, 22.0 mmol). **13f**: 0.35g (25%); mp 260-261 ^oC (decomp); IR (KBr): cm^{-1} 1648, 2205; ^1H-NMR (DMSO-d_6): δ 2.36 (3H, s, Ar-Me), 2.43 (3H, s, Me), 5.22 (2H, s, NCH_2), 6.57 and 7.33 (each 1H, s, ArH), 7.31 and 7.71 (each 2H, d, J = 7.5 Hz, ArH). *Anal*. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.68; H, 5.29; N, 10.39. **14f**: 0.78 g (52%); mp 224-225 ^oC; IR (KBr): cm^{-1} 1653; ^1H-NMR (DMSO-d_6): δ 2.41, 2.50 and 2.69 (each 3H, s, Me), 7.06 (1H, s, ArH), 7.19 (2H, s, exchangeable, NH_2), 7.37 and 8.01 (each 2H, d, J = 8.1 Hz, ArH). *Anal*. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 7.72; H, 5.76; N, 9.83.

2-(4-Methoxyphenyl)-7-methyl-5-oxo-3,5-dihydroindolizine-6carbonitrile (13g) and 3-amino-2-(4-methoxybenzoyl)-4,6-dimethylfuro[2,3-*b*]pyridine (14g)

Compounds (**13g**) and (**14g**) were prepared from the K-salt of **1** (4.66 g, 25.0 mmol) and 2-bromo-4'-methoxyacetophenone (5.73 g, 25.0 mmol). **13g**: 0.46 g (32%); mp 282-283 ^oC (decomp); IR(KBr): cm^{-1} 1650, 2207; ^1H-NMR (DMSO-d_6): δ 2.42 (3H, s, Me), 3.83 (3H, s, OMe), 5.21 (2H, s, NCH_2), 6.54 and 7.24 (each 1H, s, ArH), 6.54 and 7.79 (each 2H, d, J = 8.0 Hz, ArH). *Anal*. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.06; H, 5.10; N, 9.82. **14g**: 0.67 g (45%); mp 186-187 ^oC. IR (KBr): cm^{-1} 1607;s ^1H-NMR (DMSO-d_6): δ 2.50 (3H, s, Me), 2.69 (3H, s, Me), 7.05 (1H, s, ArH), 7.13 (2H, s, exchangeable, NH_2), 7.11 and 8.14 (each 2H, d, J = 8.8 Hz, ArH). *Anal*. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.81; H, 5.47; N, 9.36.

7-Methyl-2-(4-nitrophenyl)-5-oxo-3,5-dihydroindolizine-6-carbonitrile (13h) and 3-amino-4,6-dimethyl-2-(4-nitro-benzoyl)furo[2,3-*b*]pyridine (14h)

Compounds (**13h**) and (**14h**) were prepared from the K-salt of **1** (5.59 g, 30.0 mmol) and 2-bromo-4'-nitroacetophenone (7.96 g, 31.0 mmol). **13h**: 0.39 g (28%); mp > 270 ^{o}C. IR (KBr): cm^{-1} 1645, 2205; ^{1}H-NMR (DMSO-d_6): δ 2.50 (3H, s, Me), 5.32 (2H, s, NCH_2), 6.71 and 7.67 (each 1H, s, ArH), 8.10 and 8.32 (each 2H, d, J = 8.0 Hz, ArH). *Anal*. Calcd for $C_{16}H_{11}N_3O_3$:2H_2O: C, 65.57; H, 3.00; N, 13.90. Found: C, 63.36; H, 3.83; N, 13.12. **14h**: 0.45 g (30 %); mp 259-260 ^{o}C (decomp); IR (KBr): cm^{-1} 1645; ^{1}H-NMR (DMSO-d_6): δ 2.52 (3H, s, Me), 2.70 (3H, s, Me), 7.09 (1H, s, ArH), 7.47 (2H, s, exchangeable, NH_2), 8.27 and 8.41 (each 2H, d, J = 8.5 Hz, ArH). *Anal*. Calcd for $C_{16}H_{13}N_2O_4$·1/5H_2O: C, 61.03; H, 4.29; N, 13.34. Found: C, 61.21; H, 4.24; N, 13.13.

2-(1-Acetoxy-1-methyl)methylene-3- acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15a)

A mixture of **14a** (250 mg, 1.56 mmol), acetic anhydride (50 mL, 529.4 mmol) and pyridine (10 mL) was heated at 100 ^{o}C for 8 h. The dark solution was evaporated *in vacuo* to dryness. The residue was co-evaporated several times with EtOH and the solid residue was recrystallized from EtOH to give **15a**, 320 mg (51%); mp 98-99 ^{o}C; IR (KBr): cm^{-1} 1690, 1722; ^{1}H-NMR (DMSO-d_6): δ 2.30 (6H, s, Me and OAc), 2.38 (3H, s, Me), 2.56 (3H, s, Me), 2.57 (3H, s, NAc), 7.24 (1H, s, ArH). *Anal*. Calcd for $C_{15}H_{16}N_2O_4$·1/2H_2O C, 62.00; H, 5.63; N, 9.64. Found: C, 62.03; H, 5.64; N, 9.60.

In a similar manner as that for the synthesis of **15a**, the following compounds were prepared.

2-(1-Acetoxy-1-phenyl)methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15b)

Compound (**15b**) was synthesized from **14b** (450 mg, 1.28 mmol); yield 240 mg (58%), mp 156-157 ^{o}C; IR (KBr): cm^{-1} 1690, 1714; ^{1}H-NMR (DMSO-d_6): δ 2.33 (6H, s, Me and OAc), 2.43 (3H, s, Me), 2.60 (3H, s, NAc), 7.29 (1H, s, ArH), 7.69 (3H, m, ArH), 8.05 (2H, m, ArH). *Anal*. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.49; H, 5.23; N, 7.92.

2-[1-Acetoxy-1-(4-fluorophenyl)]methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15c)

Compound (**15c**) was synthesized from **14c** (430 mg, 1.17 mmol); yield 230 mg (41%), mp 210-211 ^{o}C; IR (KBr): cm^{-1} 1688, 1720; ^{1}H-NMR (DMSO-d_6): δ 2.33 (6H, s, Me and OAc), 2.43 (3H, s, Me), 2.60 (3H, s, NAc), 7.29 (1H, s, ArH), 7.48 (2H, t, $J_{H,H}$ = 8.0 Hz, ArH), 8.18 (2H, dd, $J_{H,F}$ = 6.4 Hz, $J_{H,F}$ = 8.0 Hz, ArH). *Anal*. Calcd for $C_{20}H_{17}N_2O_4F$: C, 65.21; H, 4.65; N, 7.61. Found: C, 65.01; H, 4.69; N, 7.53.

2-[1-Acetoxy-1-(4-chlorophenyl)]methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15d)

Compound (**15d**) was synthesized from **14d** (450 mg, 1.17 mmol); yield 440 mg (77%), mp 214-215 ^{o}C; IR (KBr): cm^{-1} 1695, 1718; ^{1}H-NMR (DMSO-d_6): δ 2.33 (6H, s, Me and OAc), 2.43 (3H, s, Me), 2.60 (3H, s, NAc), 7.29 (1H, s, ArH), 7.73 and 8.10 (each 2H, d, J = 8.4 Hz, ArH). *Anal*. Calcd for $C_{20}H_{17}$

N_2O_4Cl: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.29; H, 4.50; N, 7.20.

2-[1-Acetoxy-1-(4-bromophenyl)]methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15e)

Compound (**15e**) was synthesized from **14e** (450 mg, 1.05 mmol); yield 320 mg (57%), mp 215-216 ^oC; IR (KBr): cm^{-1} 1691, 1722; ^1H-NMR (DMSO-d_6): δ 2.33 (6H, s, Me and OAc), 2.43 (3H, s, Me), 2.60 (3H, s, NAc), 7.29 (1H, s, ArH), 7.86 and 8.01 (each 2H, d, J = 8.6 Hz, ArH). *Anal*. Calcd for $C_{20}H_{17}N_2O_4Br$: C, 55.96; H, 3.99; N, 6.53. Found: C, 55.81; H, 4.03; N, 6.39.

2-[1-Acetoxy-1-(4-methylphenyl)]methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15f)

Compound (**15f**) was synthesized from **14f** (630 mg, 1.73 mmol); yield 680 mg (85%), mp167-168 ^oC; IR (KBr): cm^{-1} 1693, 1720; ^1H-NMR (DMSO-d_6): δ 2.33 (6H, s, Me and OAc), 2.44 (6H, s, 2 x Me), 2.60 (3H, s, NAc), 7.28 (1H, s, ArH), 7.44 and 7.99 (each 2H, d, J = 7.8 Hz, ArH). *Anal*. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.24; H, 5.60; N, 7.58.

2-[1-Acetoxy-1-(4-methoxyphenyl)]methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridines (15g)

Compound (**15g**) was synthesized from **14g** (450 mg, 1.17 mmol); yield 670 mg (88%), mp 174-175 ^oC; IR (KBr): cm^{-1} 1696, 1721; ^1H-NMR (DMSO-d_6): δ 2.33 (6H, s, Me and OAc), 2.42 (3H, s, Me), 2.60 (3H, s, NAc), 3.90 (3H, s, OMe), 7.27 (1H, s, ArH), 7.17 and 8.12 (each 2H, d, J = 8.6 Hz, ArH). *Anal*. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.22; H, 5.31; N, 7.34.

2-[1-Acetoxy-1-(4-nitrophenyl)]methylene-3-acetylimino-4,6-dimethylfuro[2,3-*b*]pyridine (15h)

Compound (**15h**) was synthesized from **14h** (480 mg, 1.21 mmol); yield 430 mg (70%), mp 223-224 ^oC; IR (KBr): cm^{-1} 1685, 1721; ^1H-NMR (DMSO-d_6): δ 2.35 (6H, s, Me and OAc), 2.44 (3H, s, Me), 2.60 (3H, s, NAc), 7.31 (1H, s, ArH), 8.28 and 8.45 (each 2H, d, J = 8.7 Hz, ArH). *Anal*. Calcd for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.68. Found: C, 60.52; H, 4.33; N, 10.45.

Synthesis of furo[2,3-*b*;4,5-*b'*]dipyridine (20b-g and 24)

7,9-Dimethyl-2-hydroxy-4-phenylfuro[2,3-*b*;4,5-*b'*]dipyridine (20b)

Compound (**15b**) (700 mg, 2.0 mmol) was added into a suspension of KH (1.60 g of 33% oil suspension, 40.0 mmol) in dry toluene (80 mL, distillated from $LiAlH_4$). The reaction mixture was heated at reflux for 1 h. After cooling, diluted acetic acid (10 mL) was added into the mixture and the solution was stirred for 20 min. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to dryness. The residue was purified with liquid column chromatography (SiO_2, 3 x 20 cm, $CHCl_3$/MeOH, 50:1 v/v). The main product was collected and recrystallized from EtOH to give **20b,** 280 mg (42%); mp 286-287 ^oC, IR (KBr): cm^{-1} 1584; ^1H-NMR (DMSO-d_6): δ 2.57 (3H, s, Me), 2.85 (3H, s, Me), 6.97 (1H, s, ArH), 7.22 (1H, s, ArH), 7.55 (1H, m, ArH), 7.61 and 7.99 (each 2H, d, J = 7.6 Hz, ArH), 10.99 (1H, br, OH). *Anal*. Calcd for $C_{18}H_{14}N_2O_2 \cdot 1/8H_2O$: C, 73.89; H, 4.91; N, 9.58. Found: C,

73.99; H, 4.89; N, 9.51.

In a similar manner as that for the synthesis of **20b**, the following compounds were synthesized.

7,9-Dimethyl-4-(4-fluorophenyl)-2-hydroxyfuro[2,3-*b*;4,5-*b'*]dipyridine (20c)

Compounds (**20c**) was prepared from **15c** (200 mg, 0.54 mmol); yield 130 mg (78%); mp 290-291 ^{o}C (decomp); IR (KBr): cm^{-1} 1577; ^{1}H-NMR (DMSO-d_6): δ 2.57 (3H, s, Me), 2.86 (3H, s, Me), 6.98 (1H, s, ArH), 7.24 (1H, s, ArH), 7.46 (2H, t, $J_{H,H}$ = 8.0 Hz, ArH), 8.08 (2H, dd, $J_{H,F}$ = 6.4 Hz, $J_{H,F}$ = 8.0 Hz, ArH), 10.99 (1H, br, OH). *Anal*. Calcd for $C_{18}H_{13}N_2O_2F\cdot 1/4H_2O$: C, 70.69.11; H, 4.35; N, 8.96. Found: C, 69.18; H, 4.47; N, 8.79.

4-(4-Chlorophenyl)-7,9-dimethyl-2-hydroxyfuro[2,3-*b*;4,5-*b'*]dipyridine (20d)

Compound (**20d**) was prepared from **15d** (250 mg, 0.65 mmol); yield 170 m g (82%), mp 294-295 ^{o}C; IR (KBr): cm^{-1} 1590; ^{1}H-NMR (DMSO-d_6): δ 2.57 (3H, s, Me), 2.85 (3H, s, Me), 6.99 (1H, s, ArH), 7.22 (1H, s, ArH), 7.81 and 7.96 (each 2H, d, J = 8.6 Hz, ArH), 11.02 (1H, br, OH). *Anal*. Calcd for $C_{18}H_{13}N_2O_2Cl\cdot 4H_2O$ C, 66.57; H, 4.03; N, 8.63. Found: C, 66.456; H, 3.98; N, 8.52.

4-(4-Bromophenyl)-7,9-dimethyl-2-hydroxyfuro[2,3-*b*;4,5-*b'*]dipyridine (20e)

Compound (**20e**) was prepared from **15e** (250 mg, 0.58 mmol); yield 120 mg (58%), mp 284-285 ^{o}C; IR (KBr): cm^{-1} 1586; ^{1}H-NMR (DMSO-d_6): δ 2.57 (3H, s, Me), 2.85 (3H, s, Me), 6.99 (1H, s, ArH), 7.22 (1H, s, ArH), 7.81 and 7.96 (each 2H, d, J = 8.6 Hz, ArH), 11.02 (1H, br, OH). *Anal*. Calcd for $C_{18}H_{13}N_2O_2Br$: C, 58.55; H, 3.54; N, 7.59. Found: C, 58.33; H, 3.42; N, 7.49.

7,9-Dimethyl-2-hydroxy-4-(4-methylphenyl)furo[2,3-*b*;4,5-*b'*]dipyridine (20f)

Compound (**20f**) was prepared from **15f** (260 mg, 0.70 mmol); yield 130 mg (62%), mp 281-282 ^{o}C; IR (KBr): cm^{-1} 1588; ^{1}H-NMR (DMSO-d_6): δ 2.42 (3H, s Me), 2.57 (3H, s, Me), 3.85 (3H, s, Me), 6.96 (1H, s, ArH), 7.23 (1H, s, ArH), 7.42 and 7.92 (each 2H, d, J = 8.0 Hz, ArH), 10.92 (1H, br, OH). *Anal*. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.81; H, 5.12; N, 9.10.

7,9-Dimethyl-2-hydroxy-4-(4-methoxyphenyl)furo[2,3-*b*;4,5-*b'*]dipyridine (20g)

Compound (**20g**) was prepared from **15g** (380 mg, 1.0 mmol); yield 160 mg (88 %), mp 279-280 ^{o}C; IR (KBr): cm^{-1} 1587; ^{1}H-NMR (DMSO-d_6): δ 2.57 (3H, s, Me), 2.84 (3H, s, Me), 3.86 (3H, s, OMe), 6.94 (1H, s, ArH), 7.17 (2H, d, J = 8.4Hz, ArH), 7.22 (1H, s, ArH), 7.99 (2H, d, J = 8.4 Hz, ArH), 10.91 (1H, br, OH). *Anal*. Calcd for $C_{19}H_{13}N_2O_3$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.02; H, 5.06; N, 8.54.

4-Hydroxy-2,7,9-trimethylfuro[2,3-*b*;4,5-*b'*]dipyridine (24)

Compound (**15a**) (220 mg, 0.75 mmol) was added into a suspension of KH (510 mg of 33% oil suspension, 12.75 mmol) in dry toluene (40 mL, distillated from $LiAlH_4$). The reaction mixture was heated at reflux for 1 h. After cooling, diluted acetic acid (10 mL) was added into the mixture and the

solution was stirred for 20 min. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to dryness. The residue was purified with liquid column chromatography (SiO_2, 3 x 20 cm, $CHCl_3$/MeOH, 50:1 v/v). The main product was collected and recrystallized from EtOH to give **21**, 28 mg (6.3%); mp 290-291 ^oC; IR (KBr): cm^{-1} 1592; ^1H-NMR (DMSO-d_6): δ 2.48, 2.56 and 2.80 (each 3H, s, Me), 6.62 and 7.18 (each 1H, s, ArH), 11.02 (1H, br, OH). *Anal*. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.27. Found: C, 68.28; H, 5.22; N, 12.11.

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REFERENCES

1. R. Adams and W. Reifschneider, *J. Am. Chem. Soc*., 1959, **81**, 2537.
2. M C. Wani, P. E. Ronman, J. T. Lindley, and M. E. Wall, *J. Med. Chem*., 1980, **23**, 554.
3. K. Gewald and J. H. Jaensch1, *Journal. f. prakt. Chemie*., 1976, **318**, 313.
4. H. Jahine, H. A. Zaher, A. A. Sayed, and M. Seada, *Journal. f. prakt. Chem*ie 1974, **316**, 337.
5. R. Roberton and J. S. Watt, *J. Chem. Soc*., 1934, 1536.
6. J. Reisch, *Arch. Pharm*., 1964, **297**, 754.
7. H. R. Snyder and F. F Ebetino, *J. Heterocycl. Chem*., 1966, **3**, 202.
8. H. Sliwa, *Bull. Soc. Chim. France*, 1970, 631.
9. H. Morita and S. Schiotani, *J. Heterocycl. Chem*., 1986, **23**, 1465.