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INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF 5-NITROPYRIMIDINE WITH ENAMINES. SYNTHESIS OF 3-NITROPYRIDINE DERIVATIVES

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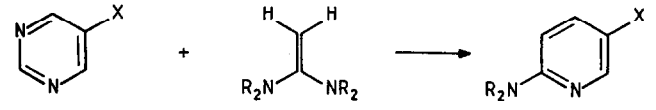
Abstract: The reaction of cyclic and non-cyclic enamines with 5-nitropyrimidine has been studied. Many enamines react in an inverse electron-demand Diels-Alder reaction, leading to the formation of 3-nitropyridines. N,S-ketene acetals were also found to react with 5-nitropyrimidine. The mechanism of the reaction will be discussed.

Recently, there has been a growing interest in inverse electron demand Diels Alder reactions with six-membered heterocycles[1]. Especially the cycloaddition reactions of 1,2,4,5-tetrazines and 1,2,4-triazines with a number of dienophiles have been studied extensively[1,2]. Cycloadditions of electron-deficient pyrimidines with ynamines, adding across the C-2 and C-5 positions are also reported[3,4]; 5-nitropyrimidines however react with ynamines in a different manner[4,5]. Recently, we found some novel intramolecular cycloadditions of pyrimidines possessing an alkyne containing side chain at position 2 or at position 5 of the pyrimidine ring, leading to bicyclic annelated pyridines[6]. In all cases cycloaddition with triple bond dienophiles occurs exclusively across the C-2 and C-5 positions.

Cycloadditions of pyrimidines with alkene dienophiles are rarely observed; in a preliminary communication the cycloaddition reactions of 5-nitropyrimidine with some enamines was reported[7].

Interestingly, the cycloadditions with enamines take place across the N-1 and C-4 positions of 5-nitropyrimidine. This preference of enamines for cycloaddition across N-1 and C-4 of 5-nitropyrimidine was correctly predicted by FMO perturbation theory[8]. In this paper we report on the inverse electron demand Diels-Alder reactions of pyrimidines with enamines with emphasis on the scope and limitations of this reaction.

Addition of enamine **2a** or **2b** to a solution of 5-nitropyrimidine **1a** in ethanol immediately gives a dark red-brown solution. After two hours at room temperature or heating at 70 °C for half an hour the 5-nitropyrimidine is completely converted into the 3-nitropyridine compounds **3a**[9] and **3b**, respectively (see Scheme 1). The structure of these compounds is firmly established by ^{1}H-NMR-, IR-, and mass spectrometric data and by elemental analysis. To explore the scope of this reaction, we reacted some other electron deficient pyrimidines with



1a; X = NO_2
b; X = SO_2CH_3
c; X = $CO_2C_2H_5$

2a; NR_2 = morpholine
b; NR_2 = piperidine

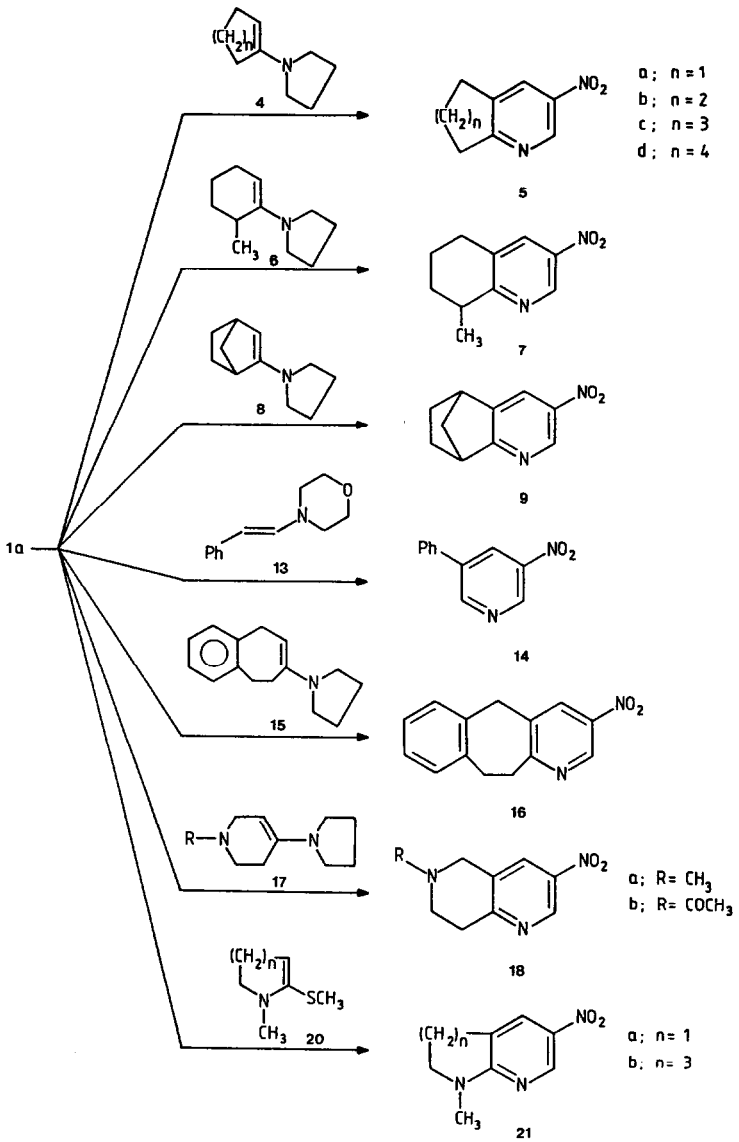
3a; X = NO_2, NR_2 = morpholine
b; X = NO_2, NR_2 = piperidine
c; X = SO_2CH_3, NR_2 = morpholine
d; X = $CO_2C_2H_5$, NR_2 = morpholine

Scheme 1

enamine **2a**. 5-Methylsulphonylpyrimidine **1b** when reacted with **2a** in refluxing ethanol for 70 h only gave a small amount of product which was identified as 5-methylsulphonyl-2-morpholinopyridine **3c**. Reaction of 5-carboethoxypyrimidine **1c** with an excess of enamine **2a** for 4 days gave only a trace of pyridine derivative **3d**. This considerable decrease in reactivity of **1b** and **1c** as compared to **1a** reflects the decreasing electron-withdrawing character of the substituent at position 5 of the pyrimidine ring. Other 5-nitropyrimidines like 4,6-dimethoxy-5-nitro-, 4-methyl-5-nitro- or 2-phenyl-5-nitropyrimidine did not react with enamine **2a**. Reaction of 4,6-dichloro-5-nitropyrimidine with **2a** resulted in the formation of 4-chloro-6-morpholino-5-nitropyrimidine[10] and 4,6-dimorpholino-5-nitropyrimidine[11]. No traces of pyridine derivatives were detected in the reaction mixture. Replacement reactions were also observed in the reaction of 2-nitropyrimidine and 2-methylsulphonyl-5-nitropyrimidine with enamine **2a**, leading to 2-morpholinopyrimidine[12] or 2-morpholino-5-nitropyrimidine[13], respectively. This type of substitution reaction of enamines has been observed before[14].

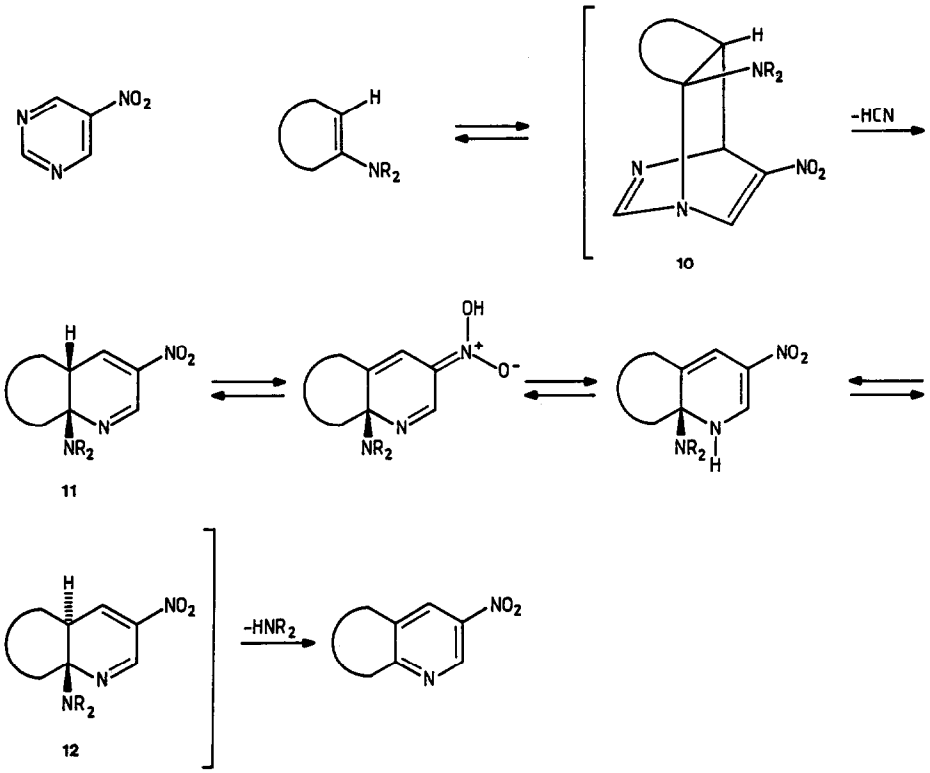
When the reaction of 5-nitropyrimidine **1a** with a tenfold excess of enamine **2a** in tetrahydrofuran at 35 °C was monitored by GLC, it was found that the reaction rate was about 8 times lower than in ethanol under the same conditions. Both the decrease of the concentration of **1a** and the increase of concentration of 2-morpholino-5-nitropyridine **3a** was measured. This result suggests a transition state of some polar character, which is not surprising[8], taking into account that we deal with a reaction between two substrates, one with electron-withdrawing and the other with electron-donating substituents. In agreement with these observations is the experimentally established fact that 1,2-bis(piperidino)ethene, a molecule which lacks dipolar character, does not react with 5-nitropyrimidine.

A very useful extension of our study, aimed to develop this new preparative methodology, was found by exploring the reaction of **1a** with cyclic enamines. It was observed that from **1a** and the five-membered enamine **4a**, the six-membered enamines **4b** and **6**, the bicyclic enamine **8**, the seven-membered enamine **4c** and the eight-membered enamine **4d**, in reasonable to good yields the [*b*]-annelated pyridines **5a-d**, **7** and **9** were obtained (see Scheme 2). The 3,5,6-substitution pattern of the pyridine is evident from the ^{1}H-NMR coupling constants of about 2.5 Hz for H-2



Scheme 2

and H-4, characteristic for a coupling between H-2 and H-4 in 3-nitropyridines. Therefore, the products must result from a regiospecific addition of the double bond of the enamine to the N-1 and C-4 atoms of 5-nitropyrimidine (see Scheme 3). Loss of hydrogen cyanide from intermediate **10** and elimination of the secondary amine from the dihydropyridine derivative **11** leads to the



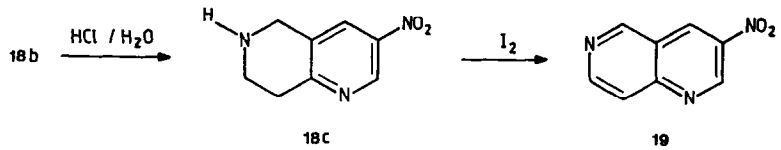
Scheme 3

3-nitropyridine derivative.

In cycloaddition reactions of enamines with tetrazines or triazines the intermediate cycloadduct or the dihydro derivatives can sometimes be identified or even isolated[15-18]; only by prolonged heating or addition of acid the dihydro derivative eliminates the amine to give the aromatic compound. In our studies we never observed the formation of a trace of intermediates **10** or **11**, although a simple E2 elimination of the secondary amine from the dihydropyridine derivatives is not expected due to the *cis* orientation of the amino group and the hydrogen in **11**[18]. Therefore, it is possible that isomerisation at C-5 in **11** occurs via tautomeric intermediates. From intermediate **12**, elimination of the secondary amine should be facile (see Scheme 3).

Reaction of 3-methyl-2-pyrrolidinocyclohexene **6** with **1a** exclusively leads to 5,6,7,8-tetrahydro-8-methyl-3-nitroquinoline **7**. The position of the methyl group is clear from a close examination of the ^{1}H-NMR spectrum of this compound. Selective irradiation shows that the H-4 signal exhibits a coupling with H-2 (2.5 Hz) and coupling with the CH_2 group on C-5 (about 2.0 Hz), thereby confirming the expected regioselectivity of this reaction. This regioselectivity is also found in the reaction of **1a** with β-morpholinostyrene **13**, yielding 3-phenyl-5-nitropyridine **14** and of the bicyclic enamine **15**, giving the tricyclic pyridine derivative **16**.

Heterocyclic enamines can also be used in the cycloaddition reactions with 5-nitropyrimidine. Reactions of the enamines of 4-piperidone **17** (R = CH_3, $COCH_3$) give good yields of the corresponding tetrahydronaphthyridines **18** (R = CH_3, $COCH_3$). The N-acetyl derivative **18b** could be hydrolyzed with 6 N hydrochloric acid to **18c** (R = H). Oxidation of this compound with iodine gave the known 3-nitro-1,6-naphthyridine **19**[19], thus also confirming the regioselectivity of the reaction (see Scheme 4).



18c 19

Scheme 4

The cyclic N,S-ketene acetals **20** (n = 1, 3) react with 5- nitropyrimidine at room temperature to give compounds **21** (n = 1, 3). These products arise from elimination of methyl mercaptan. No trace of products arising from ring opening of the saturated ring is observed; the reaction is accompanied by much decomposition and the isolated yields are low. Preferential elimination of methyl mercaptan has been observed before in cycloaddition reaction of N,S-ketene acetals[20,21]. All examples show the synthetic usefulness of the overall replacement of the C-N fragment of the pyrimidine ring by the C-C fragment of the dienophilic enamine for preparing 3-nitropyridine derivatives.

Not all enamines react with 5-nitropyrimidine. When the double bond is deactivated by an electron withdrawing substituent like in 1-morpholino-3-cyclohexenone and 2-morpholino-3-cyclohexenone no reaction occurs, being in agreement with previous observations with 1,2,4-triazines[17]. The enamine 1-dimethylamino-2-nitroethene is also unreactive with **1a**, which is not surprising since it reacts only with activated 1,2,4,5-tetrazines[22].

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-NMR spectra ($CDCl_3$) were recorded with a Varian EM-390 90 MHz spectrometer using tetramethylsilane as internal reference. ^{13}C-NMR spectra were recorded with a Bruker CXP-300 spectrometer. Mass spectra were obtained with a JEOL JMS-D-100 spectrometer. Infrared spectra were recorded on a Hitachi EPI-G3 spectrophotometer.

Starting materials

The pyrimidines 5-nitropyrimidine **1a**[23], 5-methylsulphonylpyrimidine **1b**[24], 5-carboethoxy-pyrimidine **1c**[25], 4,6-dimethoxy-5-nitropyrimidine[26], 4-methyl-5-nitropyrimidine[6], 2-phenyl-5-nitropyrimidine[27], 4,6-dichloro-5-nitropyrimidine[28], 2-nitropyrimidine[29] and 2-methyl-sulphonyl-5-nitropyrimidine[30] were prepared by published methods.

The enamines 1,1-bis(morpholino)ethene **2a**[31], 1,1-bis(piperidino)ethene **2b**[31], 1-pyrrolidinocyclopentene **4a**[32], 1-pyrrolidinocyclohexene **4b**[32], 1-pyrrolidinocycloheptene **4c**[32], 1-pyrrolidinocyclooctene **4d**[32], 3-methyl-2-pyrrolidinocyclohexene **6**[32], 2-pyrrolidinobicyclo[2,2,1]hept-2-ene **8**[33], β-morpholinostyrene **13**[34], 1,2,5,6-tetrahydro-N-methyl-4-pyrrolidinopyridine **17a**[35], N-acetyl-1,2,5,6-tetrahydro-4-pyrrolidinopyridine **17b**[36], 4,5-dihydro-1-methyl-2-(methylthio)-pyrrole **20a**[37], 4,5,6,7-tetrahydro-1-methyl-2-(methylthio)azepine **20b**[37], 1-morpholinocyclohexen-3-one[38], 2-morpholinocyclohexen-3-one[39], 1-dimethylamino-2-nitroethene **2q**[40] and 1,2-bis(piperidino)ethene[41] were also prepared by literature methods. 6,9-Dihydro-7-pyrrolidino-5*H*-benzocycloheptene **15** was prepared by the same methods from pyrrolidine and 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-one (bpt: 160°C /1 mm)[42].

General procedure for the reaction of 5-nitropyrimidine with enamines.
A solution of 250 mg of 5-nitropyrimidine (2 mmol) and 3 mmol of the appropriate enamine in 10 mL of ethanol was refluxed for 2 - 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using silica gel and the appropriate solvent system. The light yellow product was recrystallized from hexane.

2-Morpholino-5-nitropyridine (3a)
The reaction time was 2 h at room temperature. Chromatography of the residue with chloroform afforded **3a** in 57% yield; mp 143 - 144 °C (hexane/toluene); ^{1}H-NMR (deuterochloroform) δ 9.03 (d, J = 2.8 Hz, H-6), 8.24 (dd, H-4), 6.55 (d, J = 9.6 Hz, H-3), 3.80 (m, 8H).
Anal Calcd for $C_9H_{11}N_3O_3$ (M = 209.20) C, 51.67; H, 5.30. Found: C, 51.94; H, 5.21.

2-Piperidino-5-nitropyridine (3b)
The reaction time was 2 h at room temperature. Chromatography of the residue with chloroform afforded **3b** in 52% yield; mp 82 - 83 °C (hexane/ toluene); ^{1}H-NMR (deuterochloroform) δ 8.98 (d, J = 3.0 Hz, H-6), 8.08 (dd, H-4), 6.50 (d, J = 9.6 Hz, H-3), 3.7 (m, 4H), 1.65 (m, 6H).
Anal Calcd for $C_{10}H_{13}N_3O_2$ (M = 207.23) C, 57.96; H, 6.32. Found: C, 57.69; H, 6.09.

5-Methylsulphonyl-2-morpholinopyridine (3c)
The reaction time was 70 h. Chromatography of the residue with dichloromethane afforded **3c** in 20 % yield; mp 140 - 142 °C (hexane/chloroform); ^{1}H-NMR (deuterochloroform) δ 8.68 (d, J = 2.6 Hz, H-6), 7.91 (dd, J = 2.6 and 9.2 Hz, H-4), 6.64 (d, J = 9.2 Hz, H-3), 3.72 (8H), 3.04 (3H); ^{13}C-NMR (deuterochloroform) δ 160.7 (C-2), 148.8 (J = 185 Hz, C-6), 136.5 (J = 166 Hz, C-3), 124.7 (C-5), 105.2 (J = 165 Hz, C-4), 66.5, 45.3, 44.9.
Anal Calcd for $C_{10}H_{14}N_2O_3S$ (M = 242.29) C, 49.57; H, 5.82. Found: C, 49.72; H, 5.88.

6,7-Dihydro-3-nitro-5*H*-cyclopenta[*b*]pyridine (5a)
The reaction time was 2 h. Chromatography of the residue with dichloromethane afforded **5a** in 60 % yield; mp 94 - 95 °C (hexane); ^{1}H-NMR (deuterochloroform) δ 9.18 (H-2), 8.22 (H-4), 3.1 (m, 4H), 2.2 (m, 2H) .
Anal Calcd for $C_8H_8N_2O_2$ (M = 164.16) C, 58.53; H, 4.91. Found: C, 58.78; H, 5.05.

3-Nitro-5,6,7,8-tetrahydroquinoline (5b)
The reaction time was 2 h. Chromatography of the residue with dichloromethane afforded **5b** in 80 % yield; mp 71 - 72 °C (hexane); IR (KBr) 1515, 1350 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 9.18 (d, J = 2.5 Hz, H-2), 8.17 (m, H-4), 3.1-2.8 (m, 4H), 2.1 - 1.7 (m, 4H); ^{13}C-NMR (deuterochloroform) δ 164.6 (C-8a), 142.3 (C-4a), 141.9 (J = 189 Hz, C-2), 133.2 (C-3), 131.1 (J = 166 Hz, C-4), 32.9, 28.7, 22.4, 22.0.
Anal Calcd for $C_9H_{10}N_2O_2$ (M = 178.19) C, 60.66; H, 5.66. Found: C, 60.37; H, 5.61.

6,7,8,9-Tetrahydro-3-nitro-5*H*-cyclohepta[*b*]pyridine (5c)
The reaction time was 2 h. Chromatography of the residue with dichloromethane afforded **5c** in 75 % yield; mp 84 - 85 °C (hexane); IR (KBr): 1515, 1350 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 9.12 (d, J = 2.5 Hz, H-2), 8.15 (d, H-4), 3.15 (m, 2H), 2.9 (m, 2H), 2.0 - 1.5 (m, 6H); ^{13}C-NMR (deuterochloroform) δ 168.4 (C-9a), 142.9 (C-4a), 142.3 (J = 189 Hz, C-2), 137.4 (C-3), 130.9 (J = 166 Hz, C-4), 34.9, 31.9, 30.5, 25.8, 25.7.
Anal Calcd for $C_{10}H_{12}N_2O_2$ (M = 192.21) C, 62.48; H, 6.29. Found: C, 62.57; H, 6.13.

5,6,7,8,9,10-Hexahydro-3-nitro-cycloocta[*b*]pyridine (5d)
The reaction time was 2 h. Chromatography of the residue with dichloromethane afforded **5d** in 76 % yield; mp 45 - 46.5 °C (hexane); IR (KBr): 1520, 1350 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 9.21 (d, J = 2.5 Hz, H-2), 8.18 (d, H-4), 3.2 - 2.8 (m, 4H), 2.0 - 1.5 (m, 4H), 1.4 (m, 4H); ^{13}C-NMR (deuterochloroform) δ 170.2 (C- 10a), 142.7 (C-4a), 141.6 (J = 188 Hz, C-2), 139.1 (C-3), 130.6 (J = 166 Hz, C-4), 39.5, 35.0, 32.1, 27.4, 26.0.
Anal Calcd for $C_{11}H_{14}N_2O_2$ (M = 206.24) C, 64.06; H, 6.84. Found: C, 64.18; H, 6.74.

5,6,7,8-Tetrahydro-8-methyl-3-nitroquinoline (7)
The reaction time was 20 h. Chromatography of the residue with dichloromethane afforded **7** in 49 % yield; mp 67 - 68 °C (hexane); IR (KBr): 1520, 1360 cm^{-1}; 1H-NMR (deuterochloroform) δ 9.18 (d, J = 2.5 Hz, H-2), 8.12 (dt, J = 2.5 and 1.0 Hz, H-4), 3.07 (m, 1H), 2.87 (m, 2H), 2.2 - 1.5 (m, 4H), 1.38 (d, 3H); ^{13}C-NMR (deuterochloroform) δ 168.4 (C-8a), 142.1 (C-4a), 142.0 (J = 190 Hz, C-2), 132.9 (C-3), 131.1 (J = 167 Hz, C-4), 36.3,30.6, 29.3, 30.9, 19.6.
Anal Calcd for $C_{10}H_{12}N_2O_2$ (M = 192.21) C, 62.48; H, 6.29. Found: C, 62.69; H, 6.28.

5,6,7,8-Tetrahydro-5,8-methano-3-nitroquinoline (9)
The reaction time was 48 h. Chromatography of the residue with dichloromethane afforded **9** in 21 % yield; mp 117 - 118 °C (hexane); IR (KBr): 1515, 1350 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 9.12 (d, J = 2.4 Hz, H-2), 8.15 (d, H-4), 3.54 (2H), 2.2 - 1.2 (6H); ^{13}C-NMR (deuterochloroform) δ 175.6 (C-8a), 143.3 (C-4a), 142.7 (J = 189 Hz, C-2), 142.1 (C-3), 122.4 (J = 170 Hz, C-4), 48.3, 45.4, 42.5, 26.3, 24.9.
Anal Calcd for $C_{10}H_{10}N_2O_2$ (M = 190.20) C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.24; N, 14.59.

3-Nitro-5-phenylpyridine (14)
The reaction time was 24 h. Chromatography of the residue with dichloromethane afforded **14** in 28 % yield; mp 92.5 - 93.5 °C (hexane); IR (KBr): 1530, 1360 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 9.37 (d, J = 2.4 Hz, H-2), 9.08 (d, J = 2.1 Hz, H-6), 8.60 (m, H- 4), 7.7 - 7.3 (m, 5H); ^{13}C-NMR (deuterochloroform) δ 153.1 (J = 182 Hz, C-6), 144.6 (C-5), 143.3 (J = 191 Hz, C-2),

137.6 (C-3), 135.2, 129.5, 129.4, 128.9 (J = 168 Hz, C-4), 127.3.
Anal Calcd for $C_{11}H_8N_2O_2$ (M = 200.19) C, 65.99; H, 4.03. Found: C, 66.30; H, 3.97.

10,11-Dihydro-3-nitro-5*H*-benzo[4,5]cyclohepta[1,2-*b*]pyridine (16)
The reaction time was 24 h. Chromatography of the residue with dichloromethane afforded **16** in 80 % yield; mp 104 - 105 °C (hexane); IR (KBr): 1510, 1360 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ *9.18* (d, *J = 2.5 Hz, H-2), 8.26* (d, *H-4), 7.23 (4H), 4.18 (2H), 3.6 - 3.1 (4H);* ^{13}C-NMR (deuterochloroform) δ 165.9 (C-11a), 142.4 (C- 4a), 142.3 (J = 189 Hz, C-2), 139, 137.2 (C-3), 131.5 (J = 167 Hz, C-4), 129.2, 128.7, 127.8, 126.9, 39.2, 36.8, 30.4.
Anal Calcd for $C_{14}H_{12}N_2O_2$ (M = 240.25) C, 69.99; H, 5.03; N, 11.66. Found: C, 70.05; H, 5.03; N, 11.70.

5,6,7,8-Tetrahydro-6-methyl-3-nitro-1,6-naphthyridine (18a)
The reaction time was 2 h. Chromatography of the residue with ether/methanol 6 : 1 afforded **18a** in 16 % yield; mp 108 - 109 °C (hexane); IR (KBr): 1530, 1350 cm^{-1}; 1H-NMR (deuterochloroform) δ 9.22 (d, J = 2.5Hz, H-2), 8.12 (m, H-4), 3.68 (2H), 3.16 (2H), 2.83 (2H), 2.50 (s, 3H) ; ^{13}C-NMR (deuterochloroform) δ 162.0 (C-8a), 142.8 (J = 191 Hz, C-2), 142.4 (C-4a), 131.0 (C-3), 128.8 (J = 167 Hz, C-4), 56.7, 52.2, 45.7, 32.9.
Anal Calcd for $C_9H_{11}N_3O_2$ (M = 193.20) C, 55.95; H, 5.74. Found: C, 56.14; H, 5.44.

6-Acetyl-5,6,7,8-tetrahydro-3-nitro-1,6-naphthyridine (18b)
The reaction time was 3 h. Chromatography of the residue with ethylacetate/methanol 9 : 1 afforded **18b** in 48 % yield; mp 129 - 130 °C (toluene / hexane); IR (KBr): 1650 (C=O), 1520, 1350 cm^{-1}; ^{1}H-NMR (deuterochloroform) (predominant isomer) δ 9.27 (d, J = 2.5 Hz, H-2), 8.29 (d, H-4), 4.90 (2H), 3.87 (2H), 3.20 (2H), 2.22 (s, 3H) ; ^{13}C-NMR (deuterochloroform) (predominant isomer) δ 169.4, 160.7 (C-8a), 143.0 (J = 191 Hz, C-2), 129.9 (C-3), 129.3 (J = 167 Hz, C-4), 43.3, 42.9, 33.0, 21.3.
Anal Calcd for $C_{11}H_{11}N_3O_3$ (M = 221.21) C, 54.29; H, 5.01. Found: C, 54.28; H, 4.74.

2,3-Dihydro-1-methyl-5-nitropyrrolo[2,3-*b*]pyridine (21a)
The reaction time was 1 h at room temperature. Chromatography of the residue with ether afforded **21a** in 14 % yield; mp 144 - 145 °C (diisopropylether); IR (KBr): 1505, 1360 cm^{-1}; ^{1}H-NMR (deuterochloroform) δ 8.86 (d, J = 2.5 Hz, H-6), 7.83 (dt, J = 2.5 and 1.0 Hz, H-4), 3.73 (t, 2H), 3.07 (s, 3H), 3.05 (t, 2H); ^{13}C-NMR (deuterochloroform) δ 165.3 (C-7a), 147.1 (J = 185 Hz, C-6), 135.8 (C-3a), 125.1 (J = 168 Hz, C-4), 123.1 (C-5), 51.7, 31.6, 24.6.
Anal Calcd for $C_8H_9N_3O_2$ (M = 179.18) C, 53.62; H, 5.06. Found: C, 53.88; H, 4.83.

5,6,7,8-Tetrahydro-9-methyl-3-nitropyrido[2,3-*b*]azepine (21b)
The reaction time was 5 h at room temperature. Chromatography of the residue with dichloromethane afforded **21b** in 2% yield; mp 81 - 82 °C (hexane); ^{1}H - NMR (deuterochloroform) δ 8.85 (d, J = 2.5 Hz, H-2), 7.88 (d, H-4), 3.50 (m, 2H), 3.17 (s, 3H), 2.82 (m, 2H), 1.90 (m, 4H).
HRMS Calcd for $C_{10}H_{13}N_3O_2$ 207.1008 : Found: 207.1008

5,6,7,8-Tetrahydro-3-nitro-1,6-naphthyridine (18c)
A solution of 1 mmole of the acetyl compound **18b** in 15 mL of 6 N HCl was refluxed for 1.5 h.

the solution was diluted to 50 mL with water and sodium bicarbonate was added until neutral. The solution was extracted five times with 25 mL of ether. After concentration of the ether solution the residue was recrystallized from toluene/hexane. Yield 89 %; mp 116 - 117 °C (toluene/hexane); ^{1}H-NMR (deuterochloroform) δ 9.18 (d, J = 2.5 Hz, H-2), 8.10 (d, H-4), 4.13 (2H), 3.4 - 2.9 (m,4H); ^{13}C-NMR (deuterochloroform) δ 162.5 (C-8a), 142.6 (J = 189 Hz, C-2), 142.3 (C-4a), 132.2 (C-3), 128.6 (J = 167 Hz, C-4), 47.5, 43.4, 33.2.
Anal Calcd for $C_8H_9N_3O_2$ (M = 179.18) C, 52.62; H, 5.06. Found: C,55.22; H, 5.46.

3-Nitro-1,6-naphthyridine (19)
A solution of 185 mg of iodine in 15 mL of ethanol was added dropwise to a refluxing mixture of 65 mg of **18c** and 300 mg of anhydrous potassium acetate in 5 mL of ethanol. After a further 2 h of reflux, the solution was concentrated and the residue was purified by column chromatography on silica gel using ether as eluent. Yield 24 %; mp 161 - 162 °C (hexane). (Lit.19 163 - 164 °C).

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REFERENCES

1. Boger, D. L., *Tetrahedron*, **1983**, *39*, 2869; Boger, D. L., *Chem.Rev.*, **1986**, *86*, 781; Boger D. L., Weinreb, S. M., *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press,**1987**, p 300.
2. Neunhoeffer, H. in: Katritzky, A. R.; Rees, C. W. (Eds.), *Comprehensive Heterocyclic Chemistry*, Vol 3, Pergamon, **1984**, pp 422 - 429 and 550 - 555;
3. Neunhoeffer, H.; Werner, G., *Ann. Chem.*, **1974**, 1190; Martin, J. C., *J. Heterocyclic Chem.*, **1980**, *17*, 1111.
4. Marcelis, A. T. M.; van der Plas, H. C., *J. Org. Chem.*, **1986**, *51*, 67.
5. Marcelis, A. T. M.; van der Plas, H. C.; Harkema, S., *J. Org. Chem.*, **1985**, *50*, 270.
6. Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C., *Tetrahedron Lett.*, **1987**, *28*, 1589; Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C., *Recl. Trav. Chim. Pays-Bas*, **1987**, *106*, 547.
7. Charushin, V. N.; van der Plas, H. C., *Tetrahedron Lett.*, **1982**, *23*, 3965.
8. Van der Plas, H. C.; Marcelis, A. T. M.; van den Ham, D. M. W.; Verhoeven, J. W., *J. Org. Chem.*, **1986**, *51*, 4070.
9. Moore, R. G. D.; Cox, R. J., *Brit. Patent*, **1961**, 870027; *CA* **1961**, *55*: 23134.
10. Hull, R., *J. Chem. Soc.*, **1959**, 481.
11. Wiley, R. H.; Lanet, J.; Hussing, K. H., *J. Heterocyclic Chem.*, **1964**, *1*, 175.
12. Geerts, J. P.; van der Plas, H. C.; van Veldhuizen, A., *Org. Magn. Reson.*, **1975**, *7*, 86.
13. Charushin, V. N.; van der Plas, H. C. *J. Org. Chem.*, **1983**, *48*, 2667.
14. Kuehne, M. E., *J. Am. Chem. Soc.*, **1962**, *84*, 837.
15. Sauer, J.; Mielert, A.; Lang, D.; Peter, D., *Chem. Ber.*, **1965**, *98*, 1435; Reinhoudt, D. N.; Kouwenhoven, C. G., *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 321.
16. Neunhoeffer, H.; Metz, H.-J.,, *Ann. Chem.*, **1983**, 1476.

17. Boger, D. L.; Panek, J. S., *J. Org. Chem.*, **1981**, *46*, 2179; Boger, D. L.; Dang, Q., *Tetrahedron*, **1988**, *44*, 3390.
18. Chenard, B.L.; Ronau, R.T.; Schulte, G.K.; *J. Org. Chem.*, **1988**, *53*, 5175.
19. Wozniak, M.; van der Plas, H. C.; Tomula, M.; van Veldhuizen, A., *Recl. Trav. Chim. Pays-Bas*, **1983**, *102*, 359.
20. Burg, B.; Ditmar, W.; Reim, H.; Steigel, A.; Sauer, J., *Tetrahedron Lett.*, **1975**, 2897.
21. Marcelis, A. T. M.; van der Plas, H. C., *J. Heterocyclic Chem.*, **1987**, *24*, 545.
22. Marcelis, A. T. M.; van der Plas, H. C., *Heterocycles*, **1985**, *23*, 683.
23. van der Plas, H. C.; Jongejan, H.; Koudijs, A., *J. Heterocyclic Chem.*, **1987**, *15*, 485.
24. Brown, D. J.; Ford, P. W. J., *J. Chem. Soc. (C)*, **1967**, 568.
25. Bredereck, H.; Effenberger, F.; Schweizer, E. H., *Chem. Ber.*, **1962**, *95*, 803.
26. Rose, F. C.; Brown, D. J., *J. Chem. Soc.*, **1956**, 1953.
27. Barczynski, P.; van der Plas, H. C., *J. Org. Chem.*, **1982**, *47*, 1077.
28. Boon, W. R.; Jones, W. G. M.; Ramage, G. R., *J. Chem. Soc.*, **1951**, 96.
29. Taylor, E. C.; Tseng, C.-P.; Rampal, J. B., *J. Org. Chem.*, **1982**, *47*, 552.
30. Hurst, D. T.; Christophides, J., *Heterocycles*, **1977**, *6*,1999.
31. Baganz, H.; Domaschke, L., *Chem. Ber.*, **1962**, *95*, 2095.
32. Kuehne, M. E., *J. Am. Chem. Soc.*, **1959**, *81*, 5400.
33. Cook, A. G.; Meyer, W. C.; Ungrodt, K. E.; Mueller, R. H., *J. Org. Chem.*, **1966**, *31*, 14.
34. Southwick, P. C.; Kirchner, J. R., *J. Org. Chem.*, **1962**, *27*, 3305.
35. Danishefsky, S.; Cavanaugh, R., *J. Org. Chem.*, **1968**, *33*, 2959.
36. Wick, A.; Frost, J.; Bertin, J., *Fr Demande* FR 2570701; *CA* **105**: 191057t.
37. Gommper, R.; Elser, W., *Ann. Chem.*, **1969**, *725*, 64.
38. Panouse, J. J.; Sannié, C., *Bull. Soc. Chim. France*, **1956**, 1374.
39. Tobias, M. A.; Strong, J. G.; Napier, R. P., *J. Org. Chem.*,**1970**, *35*, 1709.
40. Severin, T.; Brück, B., *Chem. Ber.*, **1965**, *98*, 3847.
41. Duhamel, L.; Duhamel, P.; Plé, G., *Bull. Soc. Chim. France*, **1986**, 4423.
42. Jones, W. M.; LaBar, R. A.; Brinker, U. H.; Gebert, P. H., *J. Am. Chem. Soc.*, **1977**, *99*, 6379.