Reactivity of 2-Substituted Imidazo[1,2-*b*]pyridazines: Preparation of 3-Nitro, Nitroso and Chloro Derivatives

Maud Hervet, Christophe Galtier, Cécile Enguehard and Alain Gueiffier*

Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, 31 Avenue Monge, 37200 Tours, France

Jean-Claude Debouzy

Unité de Biophysique, Centre de Recherche du Service de Santé des Armées,
24 Avenue des Maquis du Gresivaudan, 38702 La Tronche Cedex, France
Received November 30, 2000

The synthesis of 2-substitutedimidazo[1,2-*b*]pyridazines and their reactivity towards electrophilic substitutions are reported. The nitration was shown to be very dependent on the nature of the 2 substituent. Nitrosation using sodium nitrite in acetic acid media as a general method failed in all cases whereas chlorination was observed in warm hydrochloric acid. In order to ascertain the structure of some chloro derivatives, chlorination using *N*-chlorosuccinimide was also reported. Depending of the nature of the substituent, the reaction occurred at the C-3 imidazolic position and/or at the substituent on position 2. The 3-nitroso-2-phenyl derivative was finally obtained using an alternative synthetic pathway by direct condensation of 3-amino-6-chloropyridazine to ω-chloro-ω-nitrosoacetophenone. The structural determinations were ascertained using high field ^{1}H and ^{13}C-NMR.

J. Heterocyclic Chem., **39**, 737 (2002).

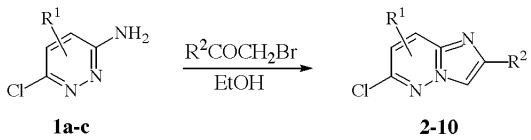
Introduction.

In continuation of our studies on the synthesis, the reactivity and the pharmacological properties of imidazolic bridgehead nitrogen heterocycles, we have recently reported the synthesis and the antiviral activity of substituted 3-aralkylthiomethyl, 3-ureido and 3-thioureidoimidazo[1,2-*b*]pyridazines [1,2]. To advance our studies to design a pharmacophore model, we were now interested in the preparation of 3-amino-2-substituted derivatives. The usual synthetic pathways use reduction with tin in hydrobromic acid of the corresponding nitro compound [3]. Surprisingly, a bibliographic research showed that electrophilic substitutions in these series were poorly studied. These works deal with the nitration and halogenation of unsubstituted derivatives in position 2 [4]. To the best of our knowledge, concerning the 2-substituted compounds only nitration and bromination of 2-methyl derivatives [4b,5] and Mannich aminomethylation, nitration and bromination of 2-aryl compounds [4c,4g] were described. Thus a general study of nitration, nitrosation and chlorination of various 2-aryl or heteroaryl derivatives was investigated.

Results and Discussion.

In order to study the influence of the substituent in position 2 on the reactivity, various 2-substituted-6-chloroimidazo-[1,2-*b*]pyridazines (**2**-**10**) were prepared by condensation of 3-amino-6-chloropyridazine derivatives (**1a**-**c**) with the appropriate α-halogenocarbonyl compound in refluxing ethanol (Scheme 1). The 3-amino-6-chloro-4- and 5-methylpyridazines **1a** and **1b** were used as a 1:10 mixture.The separation of the two isomers was performed after the cyclisation from the obtained mixture of 7- and 8-methyl-6-chloroimidazo[1,2-*b*]pyridazines derivatives.

Scheme 1



1a-c **2-10**

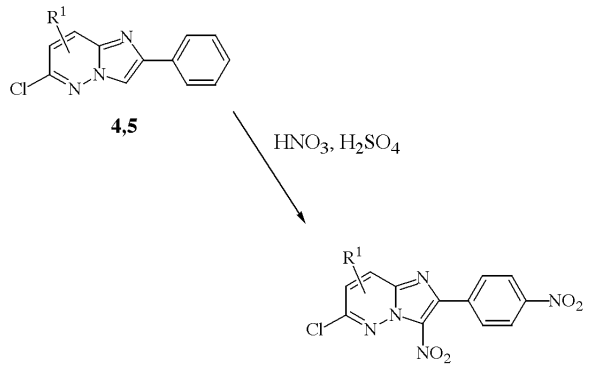
	R^1
a	4-CH_3
b	5-CH_3
c	H

	R^1	R^2
2	7-CH_3	$CO_2C_2H_5$
3	8-CH_3	$CO_2C_2H_5$
4	7-CH_3	C_6H_5
5	8-CH_3	C_6H_5
6	7-CH_3	4-ClC_6H_4
7	8-CH_3	4-ClC_6H_4
8	H	thien-2-yl
9	H	5-chlorothien-2-yl
10	H	fur-2-yl

When ethyl 6-chloro-7- and 8-methylimidazo[1,2-*b*]-pyridazine-2-carboxylate (**2**, **3**) were treated with nitric acid (d = 1.41), no reaction occurred. Under the same conditions, the 2-phenyl derivatives (**4**, **5**) led to dinitro compounds (**11**, **12**) in 90 and 70% yield respectively (Scheme 2). Proof of the structures was easily found in ^{1}H-NMR spectroscopy with the disappearance of the H-3 absorption, whereas the phenyl ring appeared as a para substituted group. The same reaction applied to the para-chloro derivatives (**6**, **7**) and thien-2-yl compound (**8**) gave a complex mixture which could not be separated. Under the same conditions, the fur-2-yl derivative (**10**) led to total degradation.

We then turned our interest to the nitrosation reaction. It is well established that in bicyclic fused imidazoles with bridgehead nitrogen atoms, the reaction occurs in the

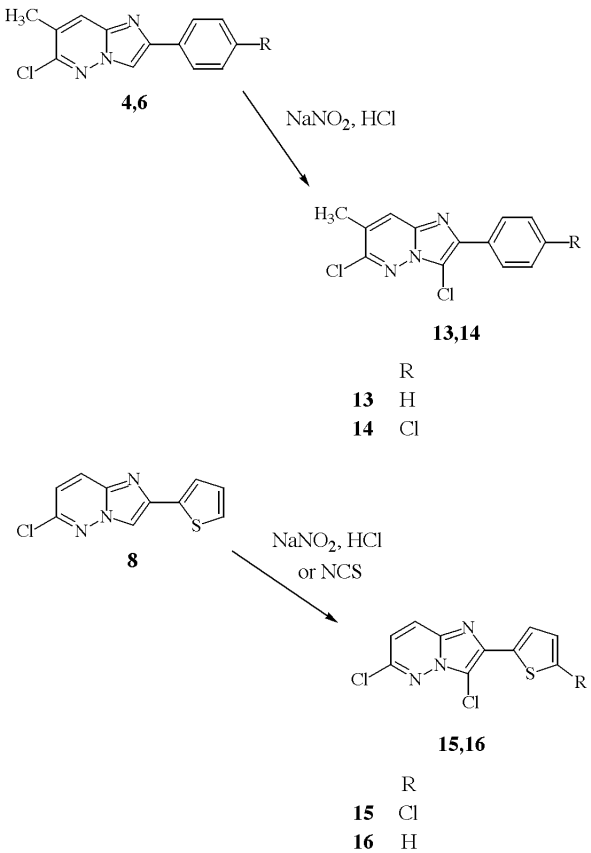
Scheme 2



	R^1
11	7-CH_3
12	8-CH_3

3-position using sodium nitrite in acetic acid media for the 2-aryl compounds [6] whereas compounds with ester groups in the same position require the use of nitrosyl chloride [7]. As expected, when the esters (**2**, **3**) were submitted to sodium nitrite in acetic acid media, no reaction occurred. Surprisingly, reaction with the 2-phenyl derivatives (**4**, **5**) failed as well. These compounds had poor solubility in acetic acid media so we decided to perform the reaction in hydrochloric acid in order to solubilize as the salt. At room temperature no reaction was found so the reaction mixture was heated at 60 °C for 3 hours. As previously observed the reaction failed with the ester whereas the phenyl derivative (**4**) led to the formation of a single product (**13**) in 25% yield (Scheme 3). The ^{1}H-NMR spectrum showed the disappearance of H-3 absorption but in ^{13}C-NMR, the absorption of C-3 at δ : 111.2 did not agree with a nitroso substitution. Furthermore no nitroso band was found in IR spectrum. Finally, the mass spectrum showed the presence of two chlorine atoms. These data allowed us to determine (**13**) as 3,6-dichloro-7-methyl-2-phenylimidazo[1,2-*b*]-pyridazine.

Scheme 3



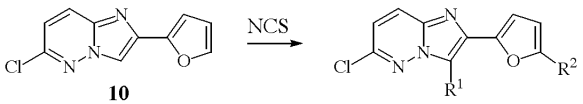
	R
13	H
14	Cl

	R
15	Cl
16	H

Further confirmation was obtained using the reaction on the *p*-chloroderivative (**6**). The same conditions led to the 3-chloro derivative (**14**) in 15% yield. When the reaction was applied to the thienyl compound (**8**) a mixture of two derivatives was obtained. The first one was determined as the 3-chloro derivative (**16**) from the ^{1}H-NMR spectrum. The second compound was identified as the trichloro derivative (**15**). The position of the last chlorine was determined from the ^{1}H-NMR spectrum. The thienyl group appeared as two doublets with a *J*-value of 4 Hz indicative of a 2,5-disubstituted derivative. Finally, the reaction was applied to the furyl compound (**10**) to give only tar materials. Since the halogenation occurred at an electrophilic position hydrochloric acid might not act as the reactant. This hypothesis was easily confirmed as no reaction occurred when (**4**) was heating at 60 °C for 3 hours in hydrochloric acid. A possible explanation is the formation of chlorine by oxidation of nitrosyl chloride formed in the experimental conditions as reported by Drozin *et al*. [8].

In order to ascertain the structure of the chloro derivatives, we decided to study the chlorination reaction. From the various reaction conditions available, we chose to use the *N*-chlorosuccinimide in chloroform media. In these conditions, the thienyl derivative (**8**) gave (**15,16**) identified by comparison with samples prepared above. Further confirmation was obtained using an unambiguous method. Thus the 5-chlorothien-2-yl compound (**9**) reacted with NCS in the same conditions to give (**15**) in 86% yield. When the reaction was attempted on the furyl derivative (**10**), a set of three compounds was obtained (Scheme 4). The major derivative (45% yield) was determined as the 3,6-dichloro derivative (**19**). The ^{1}H-NMR spectrum of (**18**) showed an H-3 absorption and the furyl group appeared as two doublets with a *J*-value of 3.6 Hz indicative of a 2,5-disubstitution. The last one (**17**) was easily demonstrated as the 3,6,5'-trichloro compound from the ^{1}H-NMR spectrum.

Scheme 4

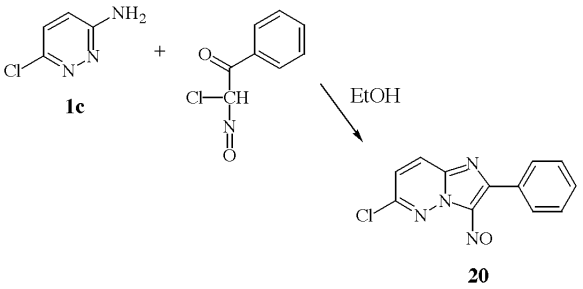


10 **17-19**

	R^1	R^2
17	Cl	Cl
18	H	Cl
19	Cl	H

In our search for a method to prepare 3-amino derivatives we then investigated another synthetic pathway. It was described that the reaction of ω-chloro-ω-nitrosoacetophenone with an α-aminonitrogen heterocycle in ethanol at room temperature gave 2-aryl-3-nitroso fused imidazole compounds [9]. Thus, this reaction was attempted on 3-amino-6-chloropyridazine (Scheme 5). Under these conditions, the expected nitroso derivative (**20**) was obtained in 68% yield (not optimized). During the preparation of this article, the use of this reaction was described by Billi *et al*., using 3-amino-6-chloropyridazine and 2-(4-chlorophenyl)-*N*-hydroxy-2-oxoethaneimidoyl chloride [10]. Proof of the structure (**20**) was found in NMR spectroscopy with the disappearance of the H-3 absorption while C-3 was shifted upfield to 153.0 ppm in agreement with Billi.

Scheme 5



1c **20**

Conclusions.

In this work, we report the synthesis and the reactivity of some 2-substitutedimidazo[1,2-*b*]pyridazines. We have shown that depending upon the nature of the substituent, the electrophilic reactions occurred at the 3-position and/or on the 2-aryl or heteroarylsubstituent. In many cases this ring system was shown to be less reactive than imidazo[1,2-*a*]-pyridines. In research directed to the preparation of 3-aminoimidazo[1,2-*b*]pyridazines we condensed ω-chloro-ω-nitrosoacetophenone with 6-chloro-3-aminopyridazine and obtained the desired nitroso compound (**20**). The scope and limitation of this method are under investigation.

EXPERIMENTAL

General Details

Melting points were determined on a Kofler Hotstage and were uncorrected. The NMR spectra were recorded on a Bruker DPX 200 or Bruker AM 400 WB spectrometers. ^{1}H-NMR chemical shifts are expressed in ppm from the residual $CHCl_3$ at 7.30 ppm or DMSO at 2.5 ppm. ^{13}C-NMR chemical shifts are given from the central resonance of $CDCl_3$ at 77.1 ppm or DMSO-d_6 at 43.5 ppm. Mass spectrum was recorded on a HP 5989A spectrometer using electronic impact at 70eV. Elemental analysis were performed by the microanalytical center, ENSCM, Montpellier, France. The 3-amino-6-chloro-4- and 5-methyl-pyridazines were synthesized according to previously described method leading to a 1:10 mixture of unseparable isomers [11]. The bromoketones were commercially available with the exception of 2-bromoacetylthiophene, 2-bromoacetyl-5-chlorothiophene and 2-bromoacetylfuran which were prepared according to previously reported methods [12-14].

General Procedure for Preparation of Imidazo[1,2-*b*]pyridazines (**2**-**10**).

A suspension of 0.069 mole of 3-amino-6-chloropyridazine **1c** or of a mixture 1:10 of 3-amino-6-chloro-4- and 5-methyl-pyridazines **1a-b** and 0.084 mole of bromoketone in 100 mL of ethanol was refluxed for 5 hours and after cooling evaporated to dryness. The residue was suspended in water, made alkaline with sodium carbonate and extracted with dichloromethane. After drying over calcium chloride, the organic layers were evaporated to dryness.

Ethyl 6-Chloro-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (**2**) and Ethyl 6-Chloro-8-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (**3**).

The residue was chromatographed on neutral alumina eluting with dichloromethane then on neutral alumina eluting with dichloromethane/petroleum ether (40:60 v/v) to give 0.995 g (6%) of **2**, mp 191 °C [Lit [15] 190-192 °C]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.46 (t, 3H, CH_3, J = 7.2Hz), 2.49 (d, 3H, CH_3, J = 1.0Hz), 4.48 (q, 2H, CH_2, J = 7.2Hz), 7.83 (br. s, 1H, 8-H), 8.41 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.8 (CH_3), 20.4 (CH_3), 61.8 (CH_2), 120.5 (3-C), 126.7 (8-C), 130.4 (7-C), 137.0 (2-C), 139.2 (8a-C), 151.0 (6-C), 163.0 (C=O).

Further elution gave 3.55 g (21%) of **3**, mp 88 °C [Lit [15] 83-85 °C]; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.37 (t, 3H, CH_3, J = 7.1Hz), 2.65 (d, 3H, CH_3, J = 1.1Hz), 4.41 (q, 2H, CH_2, J = 7.1Hz), 6.92 (d, 1H, 7-H, J = 1.1Hz), 8.33 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.7 (CH_3), 17.1 (CH_3), 61.7 (CH_2), 120.1 (7-C), 121.6 (3-C), 136.4 (2-C), 139.5 (8a-C), 141.0 (8-C), 148.9 (6-C), 162.8 (C=O).

6-Chloro-7-methyl-2-phenylimidazo[1,2-*b*]pyridazine (**4**) and 6-Chloro-8-methyl-2-phenylimidazo[1,2-*b*]pyridazine (**5**).

These compounds were separated as above to give 5.26 g (31%) of **4**, mp 193 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.45 (d, 3H, CH_3, J = 1.1Hz), 7.42 (m, 3H, 3',4',5'-H), 7.75 (q, 1H, 8-H, J = 1.1Hz), 7.95 (m, 2H, 2',6'-H), 8.15 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.2 (CH_3), 112.4 (3-C), 125.3 (8-C), 126.4 (2',6'-C), 128.1 (7-C), 128.9 (4'-C), 129.2 (3',5'-C), 133.4 (1'-C), 139.5 (8a-C), 146.4 (2-C), 148.5 (6-C).

Anal. Calcd. for $C_{13}H_{10}N_3Cl$: C, 64.06; H, 4.11; N, 17.25. Found: C, 64.15; H, 4.09; N, 17.10.

Further elution give 1.90 g (11%) of **5**, mp 160 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.73 (s, 3H, CH_3), 6.90 (s, 1H, 7-H), 7.46 (m, 3H, 3',4',5'-H), 8.00 (m, 2H, 2',6'-H), 8.19 (s, 1H, 3-H) ; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.0 (CH_3), 113.5 (3-C), 118.3 (7-C), 126.4 (2',6'-C), 128.9 (4'-C), 129.2 (3', 5'-C), 133.5 (1'-C), 139.1 (8-C), 139.6 (8a-C), 146.0 (2-C), 146.7 (6-C).

Anal. Calcd. for $C_{13}H_{10}N_3Cl$: C, 64.06; H, 4.11; N, 17.25. Found: C, 63.86; H, 4.01; N, 17.32.

6-Chloro-2-(4-chlorophenyl)-7-methylimidazo[1,2-*b*]pyridazine (**6**) and 6-Chloro-2-(4-chlorophenyl)-8-methylimidazo[1,2-*b*]-pyridazine (**7**).

These compounds were purified as for **2** and **3** to give 8.1 g (42%) of **6**, mp 181-182 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.49 (s, 3H, CH_3), 7.44 (m, 2H, 3',5'-H), 7.77 (s, 1H, 8-H), 7.89 (m, 2H, 2',6'-H), 8.14 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.3 (CH_3), 112.4 (3-C), 125.3 (8-C), 127.6 (2',6'-C), 128.4 (7-C), 129.4 (3',5'-C), 132.0 (4'-C), 134.7 (1'-C), 139.6 (8a-C), 145.3 (2-C), 148.7 (6-C).

Anal. Calcd. for $C_{13}H_9N_3Cl_2$: C, 56.11; H, 3.24; N, 15.11. Found: C, 56.20; H, 3.25; N, 15.06.

Further elution gave 8.6 g (44%) of **7**, mp 180 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.71 (d, 3H, CH_3, J = 1.1Hz), 6.90 (q, 1H, 7-H, J = 1.1Hz), 7.44 (m, 2H, 3',5'-H), 7.91 (m, 2H, 2',6'-H), 8.14 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.0 (CH_3), 113.6 (3-C), 118.5 (7-C), 127.7 (2',6'-C), 129.4 (3',5'-C), 132.0 (4'-C), 134.6 (1'-C), 139.1 (8-C), 139.6 (8a-C), 144.8 (2-C), 146.9 (6-C).

Anal. Calcd. for $C_{13}H_9N_3Cl_2$: C, 56.11; H, 3.24; N, 15.11. Found: C, 55.97; H, 3.36; N, 15.27.

6-Chloro-2-(thien-2-yl)imidazo[1,2-*b*]pyridazine (**8**).

The residue was chromatographed on neutral alumina eluting with dichloromethane to give 2.25 g (25%) of **8** mp 222-224 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.08 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.16 (dd, 1H, 4'-H, $J_{4',5'}$ = 5Hz, $J_{4',3'}$ = 3.6Hz), 7.41 (dd, 1H, 5'-H, J = 5Hz, $J_{5',3'}$ = 1.1Hz), 7.54 (dd, 1H, 3'-H, J = 3.6 Hz, J = 1.1Hz), 7.91 (d, 1H, 8-H, J = 9.4Hz), 8.15 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 112.7 (3-C), 119.5 (7-C), 125.1 (5'-C), 126.4 (8-C), 126.6 (3'-C), 128.4 (4'-C), 136.9 (2'-C), 138.2 (8a-C), 142.3 (2-C), 147.1 (6-C).

Anal. Calcd. for $C_{10}H_6N_3SCl$: C, 50.96; H, 2.55; N, 17.83. Found: C, 50.80; H, 2.54; N, 17.70.

6-Chloro-2-(5-chlorothien-2-yl)imidazo[1,2-*b*]pyridazine (**9**).

A chromatography on neutral alumina eluting with dichloromethane gave 2.1 g (15%) of **9**, mp 221-223 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.96 (d, 1H, 4'-H, $J_{3',4'}$ = 4Hz), 7.09 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.28 (d, 1H, 3'-H, J = 4Hz), 7.89 (d, 1H, 8-H, J = 9.4Hz), 8.08 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 112.6 (3-C), 119.7 (7-C), 124.1 (3'-C), 126.5 (8-C), 127.4 (4'-C), 131.3 (5'-C), 135.6 (2'-C), 138.2 (8a-C), 141.5 (2-C), 147.3 (6-C).

Anal. Calcd. for $C_{10}H_5N_3SCl_2$: C, 44.44; H, 1.85; N, 15.56. Found: C, 44.32; H, 1.78; N, 15.50.

6-Chloro-2-(fur-2-yl)imidazo[1,2-*b*]pyridazine (**10**).

This derivative was purified as above to give 6.2 g (40%) of **10**, mp 200-202 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.57 (dd, 1H, 4'-H, $J_{4',3'}$ = 3.4Hz, $J_{4',5'}$ = 1.8Hz), 6.96 (dd, 1H, 3'-H, J = 3.4Hz, $J_{3',5'}$ = 0.8Hz), 7.09 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.55 (dd, 1H, 5'-H, J = 1.8 Hz, J = 0.8 Hz), 7.90 (d, 1H, 8-H, J = 9.4Hz), 8.16 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 108.2 (3'-C), 112.2 (4'-C), 113.1 (3-C), 119.6 (7-C), 126.5 (8-C), 138.4 (8a-C), 139.2 (2-C), 143.3 (5'-C), 147.1 (6-C), 149.0 (2'-C).

Anal. Calcd. for $C_{10}H_6N_3OCl$: C, 54.67; H, 2.73; N, 19.13. Found: C, 54.82; H, 2.95; N, 19.30.

General Procedure for Nitration.

To concentrated sulfuric acid (15 mL) cooled to –10 °C was added portionwise 6.16 mmoles of the imidazopyridazine derivative (**2**-**10**) without the temperature rising above –5 °C. After complete dissolution, nitric acid (d = 1.41, 1.5 mL) was added keeping the temperature below –5 °C. The resulting mixture was stirred for further 1 hour at –10 °C then was poured on ice. The precipitate that was formed was filtered off, dried in a dessicator to give the nitro derivatives.

6-Chloro-7-methyl-3-nitro-2-(4-nitrophenyl)imidazo[1,2-*b*]pyridazine (**11**).

Compound **11** was obtained in 91% yield (1.88 g), mp 186 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.64 (d, 3H, CH_3, J = 1.1Hz), 7.99 (q, 1H, 8-H, J = 1.1Hz), 8.13 (m, 2H, 2',6'-H), 8.40 (m, 2H, 3',5'-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.2 (CH_3), 123.4 (3',5'-C), 125.7 (8-C), 130.8 (2',6'-C), 134.3 (7-C), 137.0 (1'-C), 138.3 (8a-C), 139.4 (3-C), 143.6 (2-C), 148.6 (4'-C), 151.6 (6-C).

Anal. Calcd. for $C_{13}H_8N_5O_4Cl$: C, 46.78; H, 2.40; N, 20.99. Found: C, 46.82; H, 2.38; N, 20.96.

6-Chloro-8-methyl-3-nitro-2-(4-nitrophenyl)imidazo[1,2-*b*]-pyridazine (**12**).

Compound **12** was obtained in 70% yield (1.88 g), mp 252 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.82 (d, 3H, CH_3, J = 1.1Hz), 7.35 (q, 1H, 7-H, J = 1.1Hz), 8.14 (m, 2H, 2',6'-H), 8.40 (m, 2H, 3',5'-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.8 (CH_3), 123.6 (7-C), 124.0 (3',5'-C), 131.2 (2',6'-C), 137.6 (1'-C), 138.8 (8-C), 138.9 (8a-C), 140.8 (3-C), 143.0 (2-C), 149.1 (4'-C), 150.3 (6-C).

Anal. Calcd. for $C_{13}H_8N_5O_4Cl$: C, 46.78; H, 2.40; N, 20.99. Found: C, 46.59; H, 2.37; N, 20.75.

3,6-Dichloro-7-methyl-2-phenylimidazo[1,2-*b*]pyridazine (**13**).

To a solution of 500 mg (2.05 mmoles) of 6-chloro-7-methyl-2-phenylimidazo[1,2-*b*]pyridazine (**4**) dissolved in hydrochloric acid (16 mL) was slowly added 1.4 g of sodium nitrite (20.5 mmoles) in water (1.5 mL). The mixture was heated at 60 °C for 3 hours. After cooling the solution was basified with sodium carbonate and extracted with dichloromethane. The organic layers were dried over calcium chloride then evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane to give 0.71 g (25%) of **13** as white plates, mp 234-236 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.52 (s, 3H, CH_3), 7.49 (m, 3H, 3',4',5'-H), 7.80 (s, 1H, 8-H), 8.17 (m, 2H, 2',6'-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.2 (CH_3), 111.2 (3-C), 125.5 (8-C), 127.8 (2',6'-C), 128.5 (7-C), 129.0 (3',5'-C), 129.1 (4'-C), 132.4 (1'-C), 137.9 (8a-C), 140.8 (2-C), 149.5 (6-C).

Anal. Calcd. for $C_{13}H_9N_3Cl_2$: C, 56.12; H, 3.24; N, 25.54. Found: C, 56.10; H, 3.21; N, 25.52.

2-(4-Chlorophenyl)-3,6-dichloro-7-methylimidazo[1,2-*b*]pyridazine (**14**).

This compound was obtained from 500 mg (1.80 mmoles) of 6-chloro-2-(4-chlorophenyl)-7-methylimidazo[1,2-*b*]pyridazine (**6**) according to the above procedure as white plates in 15% yield (92.2 mg); mp 228-230 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.53 (d, 3H, CH_3, J = 1.1Hz), 7.50 (m, 2H, 3',5'-H), 7.79 (q, 1H, 8-H, J = 1.1Hz), 8.13 (m, 2H, 2',6'-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.3 (CH_3), 111.2 (3-C), 125.5 (8-C), 128.9 (2',6'-C), 129.3 (3',5'-C), 130.9 (7-C), 134.3 (4'-C), 135.1 (1'-C), 137.9 (8a-C), 139.7 (2-C), 149.8 (6-C).

Anal. Calcd. for $C_{13}H_8N_3Cl_3$: C, 49.92; H, 2.56; N, 13.44. Found: C, 50.04; H, 2.68; N, 13.52.

3,6-Dichloro-2-(5-chlorothien-2-yl)imidazo[1,2-*b*]pyridazine (**15**) and 3,6-Dichloro-2-(thien-2-yl)imidazo[1,2-*b*]pyridazine (**16**).

Method A.

These compounds were obtained according to the above procedure. Separation of the crude products was made on a silica gel column eluting with dichloromethane and the derivatives were purified on silica gel using chloroform as the mobile phase.

Method B.

To a solution of 500 mg (2.12 mmoles) of **8** dissolved in chloroform (12.5 mL) was added 283 mg (2.12 mmoles) of *N*-chlorosuccinimide. The mixture was heated on a steam bath (55 °C) for 2 hours. The solvent was evaporated and the residue treated according to method A was chromatographed on neutral alumina eluting with dichloromethane then on silica gel eluting with dichloromethane to give 129 mg (20%) of **15**, mp 218 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.01 (d, 1H, 4'-H, $J_{4',3'}$ = 4Hz), 7.15 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.63 (d, 1H, 3'-H, J = 4Hz), 7.89 (d, 1H, 8-H, J = 9.4Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 111.7 (3-C), 120.0 (7-C), 125.8 (3'-C), 126.7 (8-C), 127.6 (4'-C), 132.3 (5'-C), 133.9 (2'-C), 136.8 (2-C), 137.0 (8a-C), 148.2 (6-C); ms (EI): *m/z* (%): 309 (5), 307 (36), 305 (100), 303 (99).

Anal. Calcd. for $C_{10}H_4N_3SCl_3$: C, 40.75; H, 1.36; N, 14.26. Found: C, 40.70; H, 1.40; N, 14.24.

Further elution gave 326 mg (57%) of **16**, mp 190-191 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.14 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.22 (dd, 1H, 4'-H, $J_{4',5'}$ = 5Hz, $J_{4',3'}$ = 3.7Hz), 7.49 (dd, 1H, 5'-H, J = 5Hz, $J_{5',3'}$ = 0.8Hz), 7.89 (dd, 1H, 3'-H, J = 3.7Hz, J = 0.8Hz), 7.91 (d, 1H, 8-H, J = 9.4Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 111.2 (3-C), 119.8 (7-C), 126.6 (8-C), 126.7 (3'-C), 127.4 (5'-C), 128.5 (4'-C), 135.2 (2'-C), 137.0 (8a-C), 137.7 (2-C), 148.0 (6-C).

Anal. Calcd. for $C_{10}H_5N_3SCl_2$: C, 44.44; H, 1.85; N, 15.55. Found: C, 44.45; H, 1.80; N, 15.52.

3,6-Dichloro-2-(5-chlorofur-2-yl)imidazo[1,2-*b*]pyridazine (**17**), 6-Chloro-2-(5-chlorofur-2-yl)imidazo[1,2-*b*]pyridazine (**18**) and 3,6-Dichloro-2-(fur-2-yl)imidazo[1,2-*b*]pyridazine (**19**).

These compounds were obtained according to the above general procedure from (**10**). The steam bath was heated at 45 °C for 3 hours. After a chromatography on silica gel eluting with dichloromethane, the compounds were separated on neutral alumina gel eluting with dichloromethane: petroleum ether (70: 30 v/v then 50: 50 v/v) to give 98.5 mg (15%) of **17**, mp 201-203 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.40 (d, 1H, 4'-H, $J_{4',3'}$ = 3.6Hz), 7.09 (d, 1H, 3'-H, J = 3.6Hz), 7.18 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.94 (d, 1H, 8-H, J = 9.4Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 108.9 (4'-C), 111.5 (3-C), 112.4 (3'-C), 120.2 (7-C), 127.0 (8-C), 133.6 (2-C), 137.2 (8a-C), 138.5 (5'-C), 146.3 (6-C), 148.4 (2'-C).

Anal. Calcd. for $C_{10}H_4N_3OCl_3$: C, 41.59; H, 1.39; N, 14.56. Found: C, 41.65; H, 1.50; N, 14.71.

Further elution gave 75.2 mg (13%) of **18**, mp 207-209 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.34 (d, 1H, 4'-H, $J_{4',3'}$ = 3.4Hz), 6.94 (d, 1H, 3'-H, J = 3.4Hz), 7.11 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.89 (d, 1H, 8-H, J = 9.4Hz), 8.14 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 108.9 (4'-C), 110.1 (3'-C), 113.2 (3-C), 120.0 (7-C), 126.6 (8-C), 137.4 (2-C), 138.1 (5'-C), 138.4 (8a-C), 147.3 (6-C), 148.5 (2'-C).

Anal. Calcd. for $C_{10}H_5N_3OCl_2$: C, 47.24; H, 1.97; N, 16.55. Found: C, 47.22; H, 1.96; N, 16.54.

Further elution gave 260.3 mg (45%) of **19**, mp 193-195°; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.62 (dd, 1H, 4'-H, $J_{4',3'}$ = 3.4Hz, $J_{4',5'}$ = 1.8Hz), 7.12 (dd, 1H, 3'-H, J = 3.4Hz, $J_{3',5'}$ = 0.8Hz), 7.16 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.65 (dd, 1H, 5'-H, J = 1.8Hz, J = 0.8Hz), 7.92 (d, 1H, 8-H, J = 9.4Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 110.4 (3'-C), 111.4 (3-C), 112.2 (4'-C), 119.8 (7-C), 126.9 (8-C), 134.5 (2-C), 137.1 (8a-C), 143.9 (5'-C), 146.7 (6-C), 148.1 (2'-C).

Anal. Calcd. for $C_{10}H_5N_3OCl_2$: C, 47.24; H, 1.97; N, 16.55. Found: C, 47.21; H, 2.02**;** N, 16.63.

6-Chloro-3-nitroso-2-phenylimidazo[1,2-*b*]pyridazine (**20**).

A mixture of 5 g (21.8 mmoles) of (*Z,E*)-1-chloro-2-oxo-2-phenylethanaloxime [16] and 5.6 g (43.6 mmoles) of 3-amino-6-chloropyridazine in ethanol (400 mL) was stirred for 3 hours at room temperature. The green precipitate that formed was isolated by filtration, washed with ethanol and dried in an oven to give 3.85 g (68%) of **20** as green plates, mp 244 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 7.63 (m, 3H, 3',4',5'-H), 8.18 (d, 1H, 8-H, J = 9.4Hz), 8.66 (m, 2H, 2',6'-H); ^{1}H NMR (DMSO-d_6, 400 MHz, 320 K): δ 7.66 (m, 3H, 3',4',5'-H), 8.02 (d, 1H, 7-H, $J_{7,8}$ = 9.4Hz), 8.53 (m, 2H, 2',6'-H), 8.59 (d, 1H, 8-H, J = 9.4Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, 320 K): δ 127.2 (8-C), 127.3 (3',5'-C), 127.4 (7-C), 128.5 (2',6'-C), 129.8 (4'-C), 133.6 (1'-C), 136.6 (8a-C), 147.7 (6-C), 153.0 (3-C), 157.6 (2-C).

Anal. Calcd. for $C_{12}H_7N_4OCl$: C, 55.71; H, 2.71; N, 21.66. Found: C, 55.58; H, 2.79; N, 21.75.

REFERENCES AND NOTES

[1] C. Galtier, S. Mavel, O. Chavignon, J. C. Teulade, R. Snoeck, G. Andrei, C. Pannecouque, M. Witvrouw, J. Balzarini, E. de Clercq and A. Gueiffier, *Antiviral Chem. Chemother*., 2000, accepted.

[2] A. Chaouni Ben-Abdellah, C. Galtier, H. Allouchi, A. Kherbeche, O. Chavignon, J. C. Teulade, M. Witvrouw, R. Snoeck, G. Andrei, J. Balzarini, E. de Clercq, F. Fauvelle, C. Enguehard and A. Gueiffier, *Chem. Pharm. Bull.*, **49**, 1631 (2001).

[3] Y. Blache, A. Gueiffier, O. Chavignon, H. Viols, J. C. Teulade, and J. P. Chapat, *Heterocycles*, **38**, 1527 (1994).

[4a] M. Kuwahara, Y. Kawano, H. Shimazu, Y. Ashida and A. Miyake, *Chem. Pharm. Bull*., **44**, 122 (1996); [b] J. Kobe, B. Stanovnik and M. Tisler, *Tetrahedron*, **24**, 239 (1968); [c] G. B. Barlin, L. P. Davies, S. J. Ireland, M. M. L. Ngu and

J. Zhang, *Aust. J. Chem*., **45**, 731 (1992); [d] A. S. Tomcufcik and R. G. Wilkinson, US Patent 3,711,613 (1973); *Chem. Abstr*., **78**, 115230c (1973); [e] A. S. Tomcufcik, P. T. Izzo and P. F. Fabio, US Patent 3,905,974 (1975); *Chem. Abstr.*, **84**, 4989m (1976); [f] B. Stanovnik, M. Tisler, I. Drnovsek, *Synthesis*, **12**, 987 (1981); [g] B. Stanovnik, M. Tisler, *Croat. Chem. Acta*, **40**, 1 (1968).

[5] A. E. Adam, US Patent 4,061,751 (1977); *Chem. Abstr*., **88**, 58575z (1978).

[6] J. C. Teulade, R. Escale, H. Viols, J. P. Chapat, G. Grassy, J.-M. Leger and A. Carpy, *J. Chem. Soc. Perkin. Trans I*, 2663 (1983).

[7] A. Gueiffier, J. C. Milhavet, Y. Blache, O. Chavignon, J. C. Teulade, M. Madesclaire, H. Viols, G. Dauphin and J. P. Chapat, *Chem. Pharm. Bull*., **38**, 2352 (1990).

[8] N. N. Drozin and I. S. Galinker, *Zhur. Priklad. Khim*. (*J. Appl. Chem.*), **22**, 475 (1949); *Chem Abstr.*, **44**, 1355d (1950).

[9] C. Parkanyi, A. O. Abdelhamid and J. C. S. Cheng, *J. Heterocyclic Chem*., **21**, 1029 (1984).

[10] R. Billi, B. Cosimelli, D. Spinelli, A. Andreani and A. Leoni, *Tetrahedron*, **56**, 6527 (2000).

[11] S. Linholter, A. B. Kristensen, R. Rosenørn, S. E. Nielsen and H. Kaaber, *Acta Chem. Scand*., **15**, 1660 (1961).

[12] E. Luraschi, F. Arena, A. Sacchi, S. Laneri, E. Abignente and L. Avallone, *Il Farmaco*, **52**, 213 (1997).

[13] R. Brunswig, *Chem. Ber*., **19**, 2891 (1886).

[14] S. Laufer, H. G. Striegel, K. Neher, P. Zechmeister, C. Doant, K. Stolingwa, S. Baur, S. Tries, T. Kammermeier, G. Dannhardt and W. Kiefer, *Arch. Pharm. (Weinheim)*, **330**, 9 (1997).

[15] K. Stoemer, *Liebigs Ann. Chem*., **312**, 332 (1900).

[16] A. O. Abdelhamid, S. E. Abdou and S. A. Mahgoub, *Arch. Pharm. Res*., **15**, 317 (1992).