Synthesis of 2-Substituted-3-nitroimidazo[1,2-*b*]pyridazines as Potential Biologically Active Agents

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A new heterocyclic reductive alkylating agent, 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine, was synthesized for the first time. It was shown to react under phase-transfer catalysis conditions with 2-nitropropane anion by an $S_{RN}1$ mechanism to give excellent yield of isopropylidene derivative formed from a base-promoted nitrous acid elimination of *C*-alkylation product. Extension of this $S_{RN}1$ reaction to various nitronate anions led to a new class of 3-nitroimidazo[1,2-*b*]pyridazine derivatives bearing a trisubstituted double bond at the 2-position.

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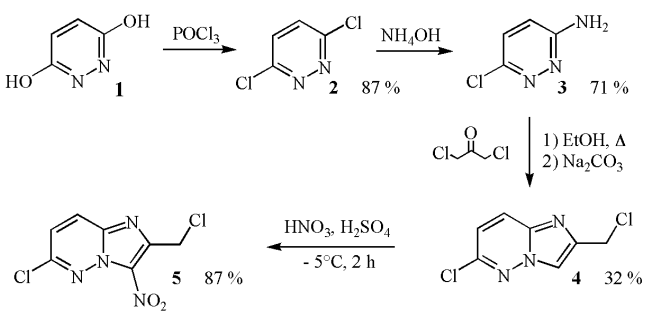
In the last decade, numerous pharmacological properties have been reported for the imidazo[1,2-*b*]pyridazine derivatives. These derivatives were shown to possess interesting biological activities such as central nervous system agents [1], antihistaminics [2] and antiasthmatics [3]. Some derivatives were also patented as herbicides [4]. Furthermore, 3-nitro derivatives have been described as antibacterial agents particularly against *Helicobacter Pylori* [5]. In light of the structure-activity relationships, reported for numerous derivatives of these compounds, the effect of substitution at position 6 was well documented. However, the nature of the substituent in position 2 was unexplored. In continuation to our studies directed toward the synthesis of new biologically active compounds [6] *via* single electron transfer reactions, we investigated the reactivity of 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]-pyridazine (**5**) with various aliphatic, cyclic or heterocyclic anions in order to prepare original 2-functionalized 3-nitroimidazo[1,2-*b*]pyridazine derivatives.

Starting with 3,6-dihydroxypyridazine (**1**), compound **5** could be easily prepared in four-steps. Thus, **1** was first converted into the corresponding dichloro derivative **2** using $POCl_3$, followed by an amination reaction with NH_4OH to form 3-amino-6-chloropyridazine (**3**) [7].

Scheme 1



The condensation of **3** with dichloroacetone led to 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine (**4**) which was converted into **5** by classical nitration using the nitrating mixture HNO_3-H_2SO_4 (Scheme 1). The reaction of 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**5**) and 3 equivalents of 2-nitropropane anion (**6**) under $S_{RN}1$ reaction conditions (inert atmosphere, light catalysis) gave only the ethylenic compound **8a**. This derivative was obtained *via* a base-promoted nitrous acid elimination of the *C*-alkylation product **7** as shown in Scheme 2.

Table 1

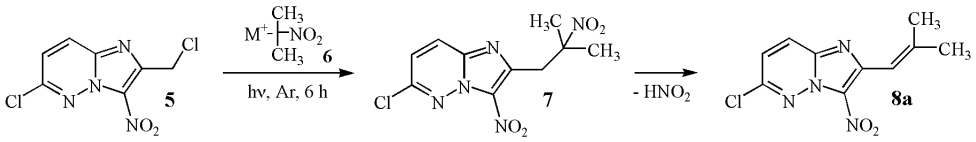
Entry [a]	M	Scavenger	Solvent	Yield **8a** (%)
1	NBu_4	-	CH_2Cl_2/H_2O	83
2	NBu_4	*p*-dinitrobenzene (1 equiv.)	CH_2Cl_2/H_2O	32
3	NBu_4	TEMPO (0.1 equiv.)	CH_2Cl_2/H_2O	11
4	NBu_4	O_2 bubbling	CH_2Cl_2/H_2O	46
5	NBu_4	Dark	CH_2Cl_2/H_2O	21
6	NBu_4	Dark, O_2 bubbling	CH_2Cl_2/H_2O	21
7	Li	-	DMF	73
8	Li	$CuCl_2$ (0.1 equiv.)	DMF	11

[a] All reactions were performed during 6 hours under argon and irradiation with a 300 W fluorescent lamp using one equivalent of imidazopyridazine (**5**) and three equivalents of 2-nitropropane anion (**6**).

The best *C*-alkylation yield was obtained under phase-transfer conditions [8] (40% tetrabutylammonium hydroxide in water and dichloromethane) with 3 equivalents of 2-nitropropane anion (**6**) during 6 hours.

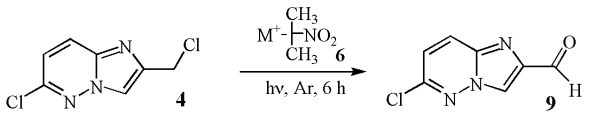
The $S_{RN}1$ mechanism was confirmed by inhibition studies [9] under optimum conditions (Table 1): addition of *p*-dinitrobenzene as radical anion scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as radical trap, $CuCl_2$ or bubbling dioxygen through the solution in the dark strongly decreased the ethylenic yield. Moreover, the

Scheme 2



importance of the nitro group has been demonstrated by the reaction of 6-chloro-2-chloromethylimidazo[1,2-*b*]-pyridazine (**4**) with 2-nitropropane anion (**6**), leading to the *O*-alkylation product **9** in a low yield and unidentifiable tarry matters (Scheme 3).

Scheme 3

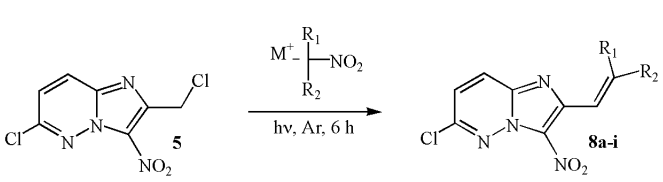


All these experimental data provide good evidence for assigning the $S_{RN}1$ mechanism to the reaction of 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**5**) and 2-nitropropane anion (**6**).

The understanding of the relationship between the nucleophile and the substrate in single electron transfer reaction is useful in order to increase the selectivity and the yield of the reaction [10], thus we have investigated the reactivity of **5** with other nitronate anions (aliphatic, cyclic, heterocyclic). The precursors of the nitronate anions were commercially available or obtained by oxidation of the corresponding amines with *m*-chloroperbenzoic acid [11]. By reacting **5** with 3 equivalents of nitronate anion under phase-transfer conditions (40% tetrabutylammonium hydroxide in water and dichloromethane), new 3-nitroimidazo[1,2-*b*]pyridazines bearing a trisubstituted ethylenic double bond at the 2-position (**8a-i**) have been prepared in moderate to good yields (Scheme 4).

These alkenes have been classically formed by electron-transfer *C*-alkylation and base-promoted nitrous acid elimination from the *C*-alkylation product. When the ethylenic derivative was unsymmetrical, the stereochemistry of the double bond has been determinated by nmr (NOESY), where the *E* isomer was found to be the only isolated product.

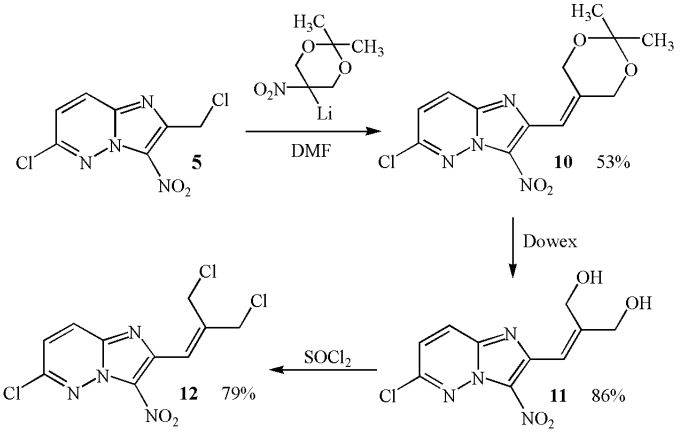
Scheme 4



a $R_1 = R_2 = CH_3$	83 %	**b** $R_1, R_2 = (CH_2)_4$	80 %
c $R_1, R_2 = (CH_2)_5$	62 %	**d** $R_1, R_2 = (CH_2)_6$	54 %
e $R_1, R_2 = (CH_2)_7$	43 %	**f** $R_1, R_2 = (CH_2)_{11}$	29 %
g $R_1 = CH_3$; $R_2 = (CH_2)_3CH(CH_3)_2$	58 %	**h** $R_1 = CH_3$; $R_2 = C_6H_5$	65 %
i $R_1 = CH_3$; $R_2 = COOCH_2CH_3$	59 %		

In order to obtain new more soluble nitroimidazo[1,2-*b*]-pyridazines, we have applied this $S_{RN}1$ reactivity with a heterocyclic nitronate anion. The 2,2-dimethyl-5-nitro-1,3-dioxane salt was prepared from the previously described (2,2-dimethyl-5-nitro-1,3-dioxan-5-yl)methanol after treatment with lithium methoxide, which induced a formaldehyde elimination [12]. The reaction of this heterocyclic nitronate anion with **5** was carried out in dimethylformamide using 3 equivalents of dioxane salt during 30 minutes to give 53% of the corresponding ethylenic compound **10**. Ring opening of derivative **10** was easily effected in methanol reflux with ion exchange resin (Dowex 50x8-50) during 24 hours to give the corresponding diol **11** in 86% yield [13]. Finally, we obtained an original bis-alkylating agent **12** by treating the diol **11** with 6 equivalents of thionyl chloride during 24 hours in 79% yield (Scheme 5).

Scheme 5



In conclusion, we have demonstrated in this paper that this methodology, based on electron transfer reactions, is a valuable and general method for the preparation of new nitroimidazo[1,2-*b*]pyridazines, of potential biological activity, under mild operating conditions.

EXPERIMENTAL

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3 and of the INP-ENSCT (Toulouse, France). Both ^1H

and ^{13}C nmr spectra were determined on a Bruker ARX 200 spectrometer. The ^{1}H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvents peaks: deuteriochloroform (76.9 ppm) or dimethylsulfoxide-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets.

Flash column chromatography was performed on silica gel 60 (Merck, particle size 0.063-0.200 mm, 70-230 mesh ASTM) and aluminium oxide (Fluka, type 507 C neutral, 100-125 mesh). Thin layer chromatography was performed on 5 x 10 cm aluminium plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.

3-Amino-6-chloropyridazine (**3**).

This compound was obtained from reaction of 3,6-dichloropyridazine (**2**) with ammonium hydroxide in 71% yield, mp 201°C [7].

6-Chloro-2-chloromethylimidazo[1,2-*b*]pyridazine (**4**).

A mixture of 3-amino-6-chloropyridazine (**3**) (5 g, 38.6 mmoles) and 1,3-dichloroacetone (4.86 g, 38.6 mmoles) in ethanol (80 ml) was heated at reflux with stirring for 4 hours. After evaporation of solvent in *vacuo*, the residue was dissolved in water (30 ml), basified with 2 *N* sodium hydroxide solution and then extracted with methylene chloride (2 x 30 ml). The organic layer was dried over anhydrous magnesium sulfate and removed under reduced pressure. The 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine (**4**) was purified by column chromatography on aluminium oxide eluting with methylene chloride and recrystallized from ethanol to give 2.5 g (32%) as a pale yellow solid; mp 154 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 4.78 (s, 2H), 7.10 (d, 1H, J = 9.4 Hz), 7.89 (d, 1H, J = 9.4 Hz), 7.98 (s, 1H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 36.5 (CH_2), 115.1 (CH), 118.3 (CH), 125.3 (CH), 136.9 (C), 144.7 (C), 146.1 (C).

Anal. Calcd for $C_7H_5Cl_2N_3$: C, 41.61; H, 2.49; N, 20.80. Found: C, 41.59; H, 2.53; N, 20.82.

6-Chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**5**).

To a solution of 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine (**4**) (2.5 g, 12.4 mmoles) in concentrated sulfuric acid (25 ml) cooled to – 10 °C was added dropwise nitric acid (d = 1.38, 2.5 ml) without allowing the temperature to rise above –5 °C. The reaction mixture was stirred at the same temperature for 2 hours, warmed to room temperature and poured into cooled water. The yellow precipitate obtained was filtered, washed with water, dried and recrystallized from ethanol to give 2.6 g (87%) of 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**5**); mp 196 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 5.14 (s, 2H), 7.52 (d, 1H, J = 9.5 Hz), 8.14 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 38.3 (CH_2), 124.5 (CH), 127.8 (CH), 137.3 (C), 145.1 (C), 150.3 (C).

Anal. Calcd for $C_7H_4Cl_2N_4O_2$: C, 34.03; H, 1.63; N, 22.68. Found: C, 34.08; H, 1.66; N, 22.64.

General Procedure for $S_{RN}1$ Reactions with Aliphatic and Cyclic Nitronate Anions.

Under nitrogen atmosphere, a solution of tetrabutylammonium hydroxide (40% in water, 1.62 ml, 2.4 mmoles) was treated with nitroalkane (2.4 mmoles) or ethyl-2-nitropropionate (0.354 g, 2.4 mmoles) for 1 hour. A solution of 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**5**) (0.2 g, 0.8 mmoles) in dichloromethane (20 ml) was added and the mixture was stirred for 6 hours at room temperature under nitrogen and irradiation with a 300 W fluorescent lamp. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed twice with water (30 ml), dried over anhydrous magnesium sulfate and removed under reduced pressure. Purification by chromatography on silica column eluting with dichloromethane and recrystallization from ethanol gave the required products (**8a-i**).

6-Chloro-2-(2-methylpropenyl)-3-nitroimidazo[1,2-*b*]pyridazine (**8a**).

This compound was obtained as an orange solid in 83% yield; mp 202 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 2.09 (s, 3H), 2.32 (s, 3H), 6.97 (s, 1H), 7.35 (d, 1H, J = 9.5 Hz), 7.94 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 21.0 (CH_3), 28.3 (CH_3), 114.2 (CH), 123.7 (CH), 126.9 (CH), 137.3 (C), 146.3 (C), 148.5 (C), 150.8 (C).

Anal. Calcd for $C_{10}H_9ClN_4O_2$: C, 47.54; H, 3.59; N, 22.18. Found: C, 47.59; H, 3.51; N, 22.16.

6-Chloro-2-cyclopentylidenemethyl-3-nitroimidazo[1,2-*b*]pyridazine (**8b**).

This compound was obtained as brown solid in 80% yield; mp 172 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.80 (m, 4H), 2.65 (t, 2H, J = 6 Hz), 2.95 (t, 2H, J = 6 Hz), 7.23 (s, 1H), 7.36 (d, 1H, J = 9.5 Hz), 7.95 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 25.7 (CH_2), 26.8 (CH_2), 33.6 (CH_2), 37.0 (CH_2), 109.8 (CH), 123.7 (CH), 126.8 (CH), 137.6 (C), 146.8 (C), 148.1 (C), 164.2 (C).

Anal. Calcd for $C_{12}H_{11}ClN_4O_2$: C, 51.72; H, 3.98; N, 20.10. Found: C, 51.71; H, 3.93; N, 20.05.

6-Chloro-2-cyclohexylidenemethyl-3-nitroimidazo[1,2-*b*]pyridazine (**8c**).

This compound was obtained as a brown solid in 62% yield; mp 150 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.67 (m, 6H), 2.41 (t, 2H, J = 5.5 Hz), 2.98 (t, 2H, J = 5.5 Hz), 6.91 (s, 1H), 7.37 (d, 1H, J = 9.5 Hz), 7.96 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.3 (CH_2), 27.9 (CH_2), 28.8 (CH_2), 30.6 (CH_2), 38.8 (CH_2), 111.2 (CH), 123.7 (CH), 126.8 (CH), 137.3 (C), 146.2 (C), 148.4 (C), 158.2 (C).

Anal. Calcd for $C_{13}H_{13}ClN_4O_2$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.28; H, 4.52; N, 19.13.

6-Chloro-2-cycloheptylidenemethyl-3-nitroimidazo[1,2-*b*]pyridazine (**8d**).

This compound was obtained as a brown solid in 54% yield; mp 152 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.57 (m, 8H), 2.54 (t, 2H, J = 5.6 Hz), 3.03 (t, 2H, J = 5.6 Hz), 7.11 (s, 1H), 7.36 (d, 1H, J = 9.5 Hz), 7.95 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.6 (CH_2), 28.6 (CH_2), 29.2 (CH_2), 29.8 (CH_2), 33.0 (CH_2), 40.0 (CH_2), 113.7 (CH), 123.6 (CH), 126.9 (CH), 137.3 (C), 146.3 (C), 148.3 (C), 161.3 (C).

Anal. Calcd for $C_{14}H_{15}ClN_4O_2$: C, 54.82; H, 4.93; N, 18.26. Found: C, 54.80; H, 4.90; N, 18.20.

6-Chloro-2-cyclooctylidenemethyl-3-nitroimidazo[1,2-*b*]pyridazine (**8e**).

This compound was obtained as a brown solid in 43% yield; mp 172 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.50 (m, 6H), 1.84 (m, 4H), 2.51 (t, 2H, J = 6 Hz), 2.97 (t, 2H, J = 6 Hz),

7.09 (s, 1H), 7.36 (d, 1H, J = 9.5 Hz), 7.95 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 25.8 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 27.1 (CH_2), 27.4 (CH_2), 31.3 (CH_2), 39.5 (CH_2), 113.7 (CH), 123.6 (CH), 126.8 (CH), 137.4 (C), 146.2 (C), 148.2 (C), 162.9 (C).

Anal. Calcd for $C_{15}H_{17}ClN_4O_2$: C, 56.16; H, 5.34; N, 17.47. Found: C, 56.11; H, 5.39; N, 17.44.

6-Chloro-2-cyclododecylidenemethyl-3-nitroimidazo[1,2-*b*]-pyridazine (**8f**).

This compound was obtained as a brown solid in 29% yield; mp 182 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.41 (m, 14H), 1.65 (m, 4H), 2.39 (t, 2H, J = 6.8 Hz), 2.89 (t, 2H, J = 6.8 Hz), 7.02 (s, 1H), 7.36 (d, 1H, J = 9.5 Hz), 7.95 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 22.2 (CH_2), 23.0 (CH_2), 23.7 (CH_2), 24.1 (CH_2), 24.2 (CH_2), 24.3 (CH_2), 24.4 (CH_2), 24.6 (CH_2), 24.8 (CH_2), 29.8 (CH_2), 33.6 (CH_2), 114.6 (CH), 123.6 (CH), 126.9 (CH), 137.2 (C), 146.5 (C), 148.4 (C), 157.5 (C).

Anal. Calcd for $C_{19}H_{25}ClN_4O_2$: C, 60.55; H, 6.69; N, 14.87. Found: C, 60.38; H, 6.57; N, 14.70.

6-Chloro-2-(2,6-dimethylhepten-1-yl)-3-nitroimidazo[1,2-*b*]-pyridazine (**8g**).

This compound was obtained as a brown solid in 58% yield; mp 102 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 0.89 (d, 6H, J = 3 Hz), 1.25 (m, 3H), 1.60 (m, 4H), 2.31 (m, 3H, J = 6 Hz), 6.98 (s, 1H), 7.37 (d, 1H, J = 9.5 Hz), 7.95 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 19.4 (CH_3), 22.5 (CH_3), 22.6 (CH_3), 25.7 (CH_2), 27.8 (CH), 38.5 (CH_2), 42.1 (CH_2), 113.7 (CH), 123.7 (CH), 126.9 (CH), 137.1 (C), 146.4 (C), 148.4 (C), 155.8 (C).

Anal. Calcd for $C_{15}H_{19}ClN_4O_2$: C, 55.81; H, 5.93; N, 17.36. Found: C, 55.72; H, 5.95; N, 17.32.

6-Chloro-3-nitro-2-(2-phenylpropenyl)imidazo[1,2-*b*]pyridazine (**8h**).

This compound was obtained as a brown solid in 65% yield; mp 234 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 2.71 (s, 3H), 7.39 (m, 5H), 7.50 (s, 1H), 7.62 (d, 1H, J = 9.5 Hz), 8.01 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 18.6 (CH_3), 115.6 (CH), 123.9 (CH), 126.5 (2xCH), 127.0 (CH), 128.5 (2xCH), 128.7 (CH), 137.4 (C), 143.1 (C), 148.8 (C), 150.0 (C), 186.2 (C).

Anal. Calcd for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.18; H, 3.55; N, 17.75.

3-(6-Chloro-3-nitroimidazo[1,2-*b*]pyridazin-2-yl)-2-methyl Acrylic Acid Ethyl Ester (**8i**).

This compound was obtained as a dark pink solid in 59% yield; mp 178 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.21 (t, 3H, J = 7.1 Hz), 2.31 (s, 3H), 4.18 (q, 2H, J = 7.1 Hz), 7.31 (d, 1H, J = 9.5 Hz), 7.92 (d, 1H, J = 9.5 Hz), 8.02 (s, 1H). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 14.2 (CH_3), 15.0 (CH_3), 61.5 (CH_2), 124.3 (CH), 124.8 (CH), 127.6 (CH), 137.3 (C), 138.7 (C), 143.2 (C), 149.6 (C), 167.7 (C).

Anal. Calcd for $C_{12}H_{11}ClN_4O_4$: C, 46.39; H, 3.57; N, 18.03. Found: C, 46.34; H, 3.59; N, 18.01.

Influence of Electron-withdrawing Group.

The procedure was similar to that for using 6-chloro-2-chloromethylimidazo[1,2-*b*]pyridazine (**4**) (0.145 g, 0.8 mmoles) and 2-nitropropane (0.215 g, 2.4 mmoles). After work up and purification, the 6-chloro-2-formylimidazo[1,2-*b*]pyridazine (**9**) was obtained as a yellow solid in 5% yield; mp 120 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 7.19 (d, 1H, J = 9.5 Hz), 8.00 (d, 1H, J = 9.5 Hz), 8.44 (s, 1H), 10.15 (s, 1H).

Anal. Calcd for $C_7H_4ClN_3O$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.22; H, 2.18; N, 23.11.

Inhibited Reaction of **5** with 2-Nitropropane (**6**) (Table 1).

The procedure was similar to that of the general procedure except that the inhibitor was added to the reaction mixture immediately prior to the chloride **5**. The study in the dark was obtained by wrapping the flask in aluminium foil. The inhibition study with molecular oxygen was carried out by replacing nitrogen with oxygen.

6-Chloro-2-(2,2-dimethyl[1,3]dioxan-5-ylidenemethyl)-3-nitroimidazo[1,2-*b*]pyridazine (**10**).

2,2-Dimethyl-5-nitro-1,3-dioxane salt (0.405 g, 2.42 mmoles) was added to a solution of 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**5**) (0.2 g, 0.8 mmoles) in dry dimethylformamide (30 ml). The reaction was allowed to proceed for 6 hours at room temperature under nitrogen and in the presence of light (300 W fluorescent lamp). After stirring, the reaction mixture was removed under reduced pressure. The residue was dissolved in dichloromethane (40 ml), washed with water (2 x 30 ml), dried over anhydrous magnesium sulfate and removed under reduced pressure. Purification by chromatography on silica gel eluting with dichloromethane and recrystallization from ethanol gave 6-chloro-2-(2,2-dimethyl[1,3]dioxan-5-ylidenemethyl)-3-nitroimidazo[1,2-*b*]pyridazine (**10**) as a brown solid in 53% yield; mp 176 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 1.45 (s, 6H), 4.48 (s, 2H), 5.07 (s, 2H), 7.04 (s, 1H), 7.40 (d, 1H, J = 9.5 Hz), 7.98 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 24.0 (2xCH_3), 62.4 (CH_2), 64.0 (CH_2), 99.9 (C), 110.4 (CH), 124.1 (CH), 127.1 (CH), 137.4 (C), 144.3 (C), 148.9 (C), 152.0 (C).

Anal. Calcd for $C_{13}H_{13}ClN_4O_4$: C, 48.08; H, 4.04; N, 17.25. Found: C, 48.01; H, 4.09; N, 17.18.

2-(6-Chloro-3-nitroimidazo[1,2-*b*]pyridazin-2-ylmethylene)-propane-1,3-diol (**11**).

A stirred mixture of 6-chloro-2-(2,2-dimethyl-[1,3]dioxan-5-ylidenemethyl)-3-nitroimidazo[1,2-*b*]pyridazine (**10**) (1.5 g, 4.6 mmoles) and 0.32 g of ion-exchange resin (Dowex 50x8-50, Aldrich) in methanol (75 ml) was refluxed for 24 hours. After filtration of the resin and evaporation under reduced pressure, the residue was purified by recrystallization from ethanol to give 1.13 g (86% yield) of 2-(6-chloro-3-nitroimidazo[1,2-*b*]-pyridazin-2-ylmethylene)propane-1,3-diol (**11**) as an orange solid; mp 166 °C. ^{1}H nmr (dimethylsulfoxide-d_6, 200 MHz): δ 3.15-3.55 (br, 2H, OH), 4.34 (s, 2H, CH_2), 4.68 (s, 2H, CH_2), 7.25 (s, 1H, CH), 7.85 (d, 1H, J = 9.1 Hz), 8.46 (d, 1H, J = 9.1 Hz). ^{13}C nmr (dimethylsulfoxide-d_6, 50 MHz): δ 59.6 (CH_2), 62.5 (CH_2), 110.8 (CH), 125.3 (CH), 128.4 (CH), 138.3 (C), 144.9 (C), 148.3 (C), 157.1 (C).

Anal. Calcd for $C_{10}H_9ClN_4O_4$: C, 42.19; H, 3.19; N, 19.68. Found: C, 42.08; H, 3.26; N, 19.63.

6-Chloro-2-(3-chloro-2-chloromethylpropenyl)-3-nitroimidazo[1,2-*b*]pyridazine (**12**).

Thionyl chloride (0.8 ml, 10.5 mmoles) was added dropwise to a solution of (**11**) (0.5 g, 1.75 mmoles) in dry dichloromethane (10

ml) in a round-bottomed flask equipped with a reflux condenser surmounted by a calcium chloride drying tube. After stirring at room temperature for 24 hours, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in water (20 ml), the aqueous solution was then basified with saturated sodium bicarbonate solution. Extraction with dichloromethane (2 x 20 ml), drying of the extracts over anhydrous magnesium sulfate, removal of the solvent under reduced pressure and recrystallization of the product from ethanol gave 0.44 g (79% yield) of 6-chloro-2-(3-chloro-2-chloromethylpropenyl)-3-nitroimidazo[1,2-*b*]pyridazine (**12**) as a brown solid; mp 144 °C. ^{1}H nmr (deuteriochloroform, 200 MHz): δ 4.48 (s, 2H), 5.14 (s, 2H), 7.43 (s, 1H), 7.46 (d, 1H, J = 9.5 Hz), 8.06 (d, 1H, J = 9.5 Hz). ^{13}C nmr (deuteriochloroform, 50 MHz): δ 39.4 (CH_2), 47.1 (CH_2), 120.4 (CH), 124.6 (CH), 127.6 (CH), 137.3 (C), 142.0 (C), 143.8 (C), 149.8 (C).

Anal. Calcd for $C_{10}H_7Cl_3N_4O_2$: C, 37.35; H, 2.19; N, 17.42. Found: C, 37.27; H, 2.24; N, 17.35.

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