Carbon Disulfide Promoted Reactions of 2-Chloro-4,5-dihydro-imidazole with Some *N*-Nucleophiles

Franciszek SĄCZEWSKI,*[,a] Jarosław SĄCZEWSKI,[a] and Maria GDANIEC[b]

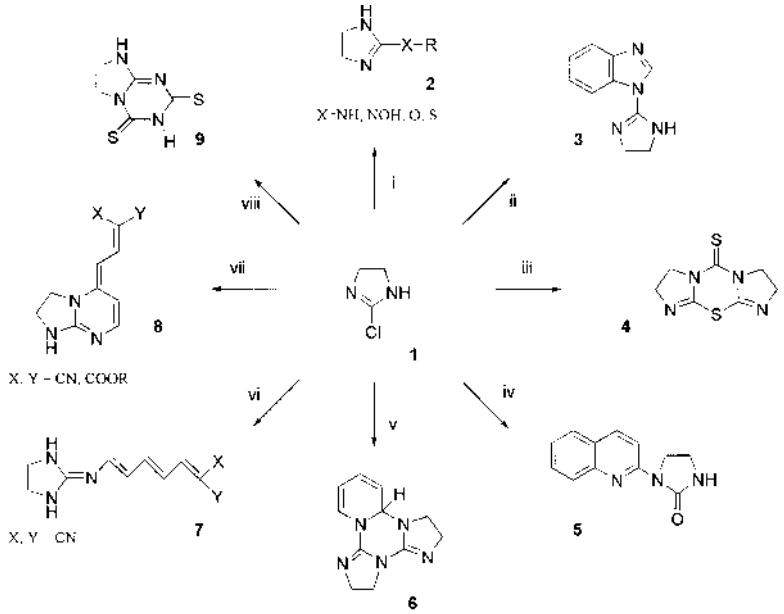
Department of Chemical Technology of Drugs, Medical University of Gdańsk,[a] 80–416 Gdańsk, Poland and Faculty of Chemistry, A. Mickiewicz University,[b] 60–780 Poznań, Poland. Received March 14, 2001; accepted May 7, 2001

The reactions of 2-chloro-4,5-dihydroimidazole 1 with *o*-substituted anilines and azoles promoted by carbon disulfide have been carried out. *Ab initio* MO calculations were used to elucidate the mechanism of the reaction of 1 with *N*-nucleophilic reagents. A facile synthesis of 2-(4,5-dihydroimidazol-2-yl)-1*H*-indazole 3e bearing structural resemblances to 2-BFI, a potent and selective agonist of imidazoline I_2 receptors, is also described. Structure of 3e was confirmed by NMR spectroscopy and X-ray analysis.

Key words 2-chloro-4,5-dihydroimidazole; carbon disulfide; nucleophilic substitution; *N*-nucleophiles; 2-(4,5-dihydroimidazol-2-yl)-1*H*-indazole; X-ray analysis

2-Chloro-4,5-dihydroimidazole **1** was first synthesized by Trani and Belasio in 1974[1] and since then has been widely used for the synthesis of various 2-imidazoline derivatives of pharmacological importance as exemplified in Chart 1. Displacement of the chlorine with nucleophilic reagents such as amines, hydroxylamines, phenols and thiophenols leads to the formation of 2-substituted products **2**.[1—10] Compounds of this type, and especially 2-arylimino-imidazolidines are known to interact with α-adrenergic receptors[11] and the recently discovered imidazoline receptors.[12] Clinical uses, which explain the interest in new and better strategies for the construction of these compounds, include: hypertension, modulation of pituitary hormone release, depression, Alzheimer's disease, Raynauld phenomenon, noninsulin-dependent diabetes, obesity, and impotence.[13] Recent research by our group using compound **1** includes syntheses of *N*-(4,5-dihydroimidazol-2-yl-azoles **3**,[14] diimidazo[2,1-*b*:1′,2′-*e*][1,3,5]thiadiazine-5-thione **4**,[15] 1-heteroaryl-imidazolilidine-2-ones **5**,[16] pyrido[1,2-*a*]diimidazo[1′,2′-*c*:1″,2″-*e*]-[1,3,5]triazines **6**,[17] imidazol-2-ylideneamino-hexa-1,3,5-triene-1,1-dicarbonitriles **7**,[18] imidazo[1,2-*a*]pyrimidines **8**[19] and imidazo[1,2-*a*][1,3,5]triazine-2,4-dithione **9**[20] (Chart 1).

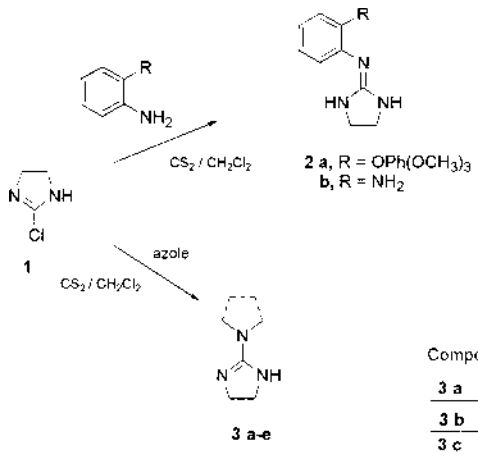
2-Chloro-4,5-dihydroimidazole **1** itself proved to be extremely unstable, and therefore, it has to be stored in the form of a hemisulfate or hydrochloride salt.[1] The reactions of **1** with nucleophilic reagents should be carried out under mild conditions (room temperature) and usually require 8—42 h for their completion.[3,5,7] On the other hand, compound **1** possesses a nucleophilic centre at the *N*-3 nitrogen atom and tends to react with one another giving rise to the formation of self-condensation products.[1] Such a side reaction prevails when a reaction of **1** with a weak nucleophile is carried out



Reagents: i) amine, hydroxylamine, phenolate or thiophentolate; ii) azole, CH_3CHO; iii) CS_2, Et_3N; iv) quinoline-N-oxide or isoquinoline-N-oxide; v) pytidine or isoquinoline; vi) pyridine, CH-acid; vii) DMAP, CH-acid; viii) NH_4SCN;

Chart 1

* To whom correspondence should be addressed. e-mail: saczew@farmacja.amg.gda.pl



Compd.	Reaction time / Yield / [Ref.] non-promoted	CS_2 promoted
2a	42 h / 49% [3]	3 h / 65%
2b	12 h / 37% [7]	0.5 h / 61%

Compd.		Yield %
3 a	imidazol-1-yl	84
3 b	benzimdazol-1-yl	76
3 c	pyrazol-1-yl	75
3 d	benzotriazol-1-yl	61
3 e	indazol-2-yl	67

Chart 2

under vigorous conditions (elevated temperature).

Now we wish to describe carbon disulfide promoted reactions of **1** with various *N*-nucleophilic reagents such as *o*-substituted aromatic amines and azoles, which are high yielding and much faster than the previously reported techniques for preparation of the same compounds.

Results and Discussion

Our study was initiated by examining the reactivity of **1** with sterically hindered *o*-substituted anilines in the presence of carbon disulfide. It has been previously reported that the reaction of **1** with 2-(3,4,5-trimethoxyphenoxy)aniline required 42 h at room temperature to provide the desired arylliminoimidazolidine **2a**.[3] We found that the same reaction could be accomplished within 3 h by using of 0.13 molar equivlent of carbon disulfide and afforded **2a** in good yield. Analogous reaction of **1** with *o*-phenylenediamine proceeded exothermically and required 0.5 h for its completion (Chart 2).

The compound **1** does not react with azoles such as imidazole, benzimidazole, pyrazole, benzotriazole or indazole, due to the fact that the nucleophilicity of azoles towards **1** is low. We previously succeeded in synthesizing *N*-(4,5-dihydro-imidazol-2-yl)azoles by making use of the reaction of **1** with azole adducts to aliphatic aldehydes.[14] However, in this method the reaction with benzotriazole or indazole hemiaminal the mixtures of benzotriazol-1-yl and benzotriazol-2-yl as well as indazol-1-yl and indazol-2-yl isomers are formed. A similar pattern was also observed in other *N*-alkylation reactions of these heterocycles.[21]

We now have used carbon disulfide as catalyst and found that the reaction of **1** with azoles is very general and in all cases the *N*-substituted azoles were obtained as a one positional isomer (Chart 2). Thus, with respect to benzotriazole and indazole, the heteroalkylation process was found to be completely regioselective in nature and no *N*-2 substituted benzotriazole or *N*-1 substituted indazole derivative was isolated.

It is worth noting that several different Lewis acids (*e.g.* $BF_3 \cdot Et_2O$ or $TiCl_4$) were surveyed, but all failed to induce the nucleophilic substitution of chlorine by azole.

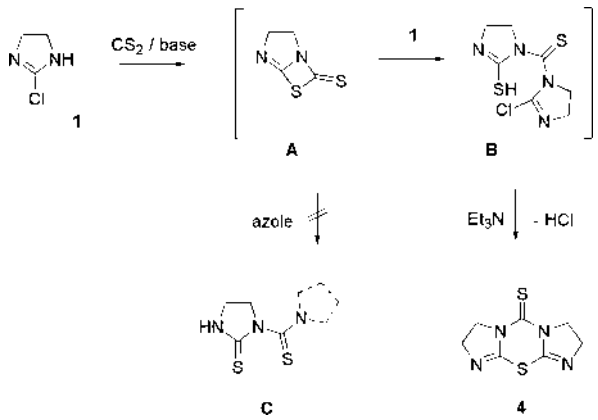


Chart 3

Previously we found that the compound **1** reacts with carbon disulfide in the presence of triethylamine to give diimidazo[2,1-*b*:1′,2′-*e*][1,3,5]thiadiazine **4**.[15] We proposed that in this process the imidazothiazetedine **A** is formed transiently and subsequently reacts with a second molecule of **1** yielding the cyclic derivative **4** (Chart 3). However, when the reaction of **1** with carbon disulfide is carried out in the presence of an azole, instead of triethylamine, no product of type **C** is formed (Chart 3).

To elucidate the mechanism of the reaction of **1** with azoles, we estimated the possible reactivity of the intermediate A with **1** and indazole using *ab initio* MO calculations.[22] Atomic charges, electrostatic potentials and absolute values of HOMO and LUMO mapped on the van der Waals contact surfaces are shown in Fig. 1.

As seen, the carbon atom C-2 in A (LUMO＝0.305 a.u.) is more active than the C-4 (LUMO＝0.0118 hartree), and therefore, the orbital-controlled reaction with *N*-3 nitrogen atom of **1** (HOMO＝0.0277 a.u.) is possible. On the other hand, the possibility of electrostatically-controlled reaction at C-2 of **A** is belived to be very low due to its negative charge.

Analogous reaction of the intermediate **A** with indazole leading to compound **C** (Chart 3) was not observed in spite of the large coefficient value in the HOMO at *N*-1 nitrogen

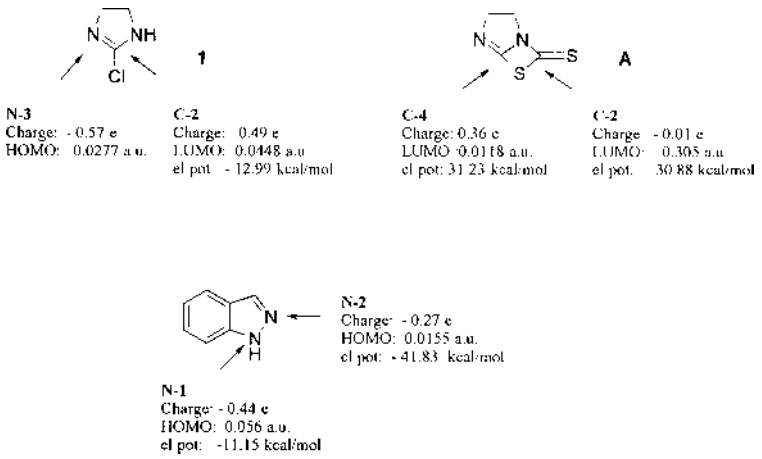


Fig. 1

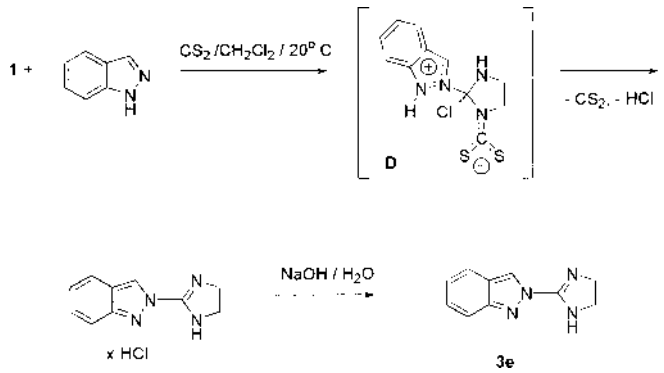


Chart 4

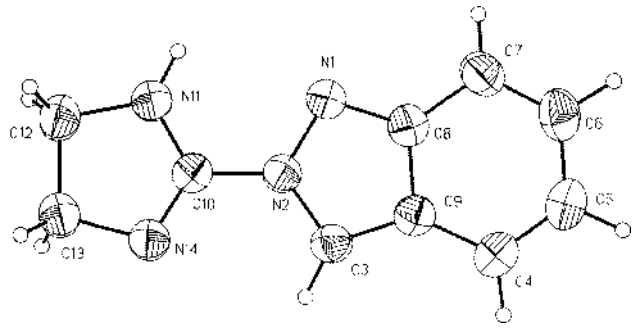


Fig. 2. ORTEP Drawing of **3e**

atom (HOMO=0.056 a.u.). Therefore, as a possible mechanism for the above discussed reaction we can advance the hypothesis that **1** reacts with azoles to yield the general adduct **D** which, in turn, undergoes further stabilization with concominant release of carbon disulfide and formation of product **3** as depicted in Chart 4. Carbon disulfide accelerates the reaction mainly by stabilization of the intermediate **D** which contains the electron stabilizing dithiocarbamate group. In absence of carbon disulfide, this stabilization is lost and the barrier for the reaction is higher.

It is pertinent to note that the newly prepared indazole derivative **3e** represents an interesting analog of 2-(4,5-dihydroimidazol-2-yl)benzofurane (2-BFI) which is known to be a potent and selective agonist of the imidazoline I_2 receptors.[23] The structure of **3e** has been confirmed using spectroscopic data and by X-ray analysis (Fig. 2).

An interesting feature of the ^{1}H-NMR spectrum of **3e** is the presence of two distinct multiplets at 3.7 and 4.05 ppm attributable to CH_2–CH_2 grouping of 2-substituted imidazoline ring. In ^{13}C-NMR spectrum two signals at 45.79 and 54.57 ppm appear for the two corresponding carbon atoms. Such a pattern is indicative of a strong intramolecular hydrogen bonding between imidazoline N–H group and indazole N-1 atom in $CDCl_3$ solution, which hinders the tautomeric process within the amidine moiety. The *E* conformation of **3e** is further confirmed by a strong deshielding C3–H effect as the signal for this proton appears at 8.74 ppm.

The 3-D electrostatic potential maps (Fig. 3) clearly show that heteroatoms in both 2-BFI and indazole analogue **3e** are surrounded by a negative envelope at −20 kcal/mol with similar shape and the absolute minimum lying near the *N*-3 nitrogen atom of 2-imidazoline ring.

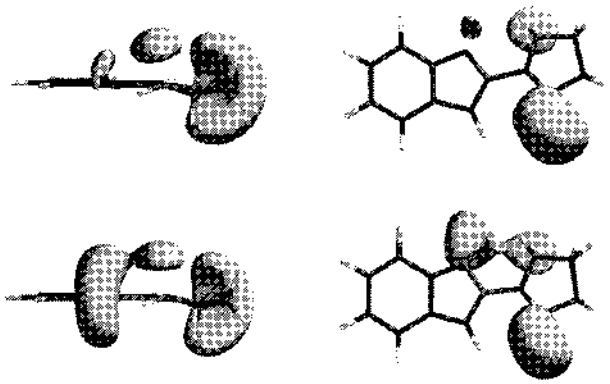


Fig. 3. *Ab initio* 3-D Electrostatic Potential Isocontoured at −20 kcal/mol for the 6-31G** Optimized Structures of 2-BFI (Top) and **3e** (Bottom)

Experimental

Melting points (mp) were determined on a Buchi 535 apparatus without correction. Infrared (IR) spectra (KBr pellet) were measured by a Perkin Elmer FT-IR 1600. ^{1}H- and ^{13}C-Nuclear magnetic resonance (NMR) spectra were obtained at ambient temperature with a Varian XL 200 spectrophotometer in DMSO-d_6 or $CDCl_3$, with tetramethylsilane as an internal standard. Compound **1** was obtained according to the procedure described in ref. 1.

Reaction of (1) with 2 (3,4,5-Trimethoxyphenoxy)aniline To a stirred solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 ml) was added carbon disulfide (0.2 ml, 3.3 mmol) and 2-(3,4,5-trimethoxyphenoxy)aniline (6.5 g, 24 mmol). After the slightly exothermic reaction had subsided (3 h), the reaction mixture was treated with Et_2O (10 ml) and the solid that precipitated was collected by filtration. Then, the crude hydrochloride was dissolved in water (15 ml) and the solution was made alkaline (pH=10) with 10% aqueous NaOH followed by extraction with CH_2Cl_2. After evaporation of solvent, the compound **2a** thus obtained was purified by crystallization from ethyl acetete/ethanol. Yield: 5.3 g, 65%; mp 146—149 °C (ref. 3, mp 147—150 °C).

Reaction of (1) with *o*-Phenylenediamine A solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 ml) was treated with carbon disulfide (0.2 ml, 3.3 mmol) and the reaction mixture was stirred for 5 min at room temperature. Then, *o*-phenylenediamine (2.6 g, 24 mmol) was added and stirring was continued untill the vigorous exothermic reaction had subsided (0.5 h). Solvent was evaporated under reduced pressure and the oily residue was triturated with acetone. The crude hydrochloride that precipitated was collected by filtration, dissolved in water (10 ml) and the resulting solution was made alkaline (pH=10) with 10% aqueous NaOH. The solid product obtained was separated by suction, washed with cold water and purified by crystallization from EtOH to give **2b** (2.1 g, 61%), mp 156—158 °C (ref. 7, mp 155—158 °C).

2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1*H*-indazole (3e) To a solution of **1** (2.5 g, 24 mmol) in CH_2Cl_2 (30 ml) was added carbon disulfide (0.2 ml, 3.3 mmol) and indazole (3.5 g, 30 mmol) and the reaction mixture was stirred at room temperature for 6 h. The solid that precipitated was separated by suction and recrystallized from EtOH to give **3e**·HCl (3.6 g, 67%); mp 141—144 °C. IR ν_{max} (KBr) cm^{-1}: 3066, 2957, 2764, 1640, 1614, 1386, 1335, 1292, 1254, 1207, 1126, 1032. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 4.08 (s, 4H, CH_2), 7.25 (t, 1H, arom.), 7.5 (t, 1H, aromat.), 7.75 (d, 1H, aromat.), 7.85 (d, 1H, arom.), 9.57 (s, 1H, arom.), 11.55 (br s, 2H, NH). Free base **3e** was obtained by treatment of an aqueous solution of the hydrochloride described above with 10% aqueous NaOH at 5 °C and recrystallization of the resulting precipitate from acetone; mp 131—132 °C. IR ν_{max} (KBr) cm^{-1}: 3248, 3132, 2874, 1634, 1531, 1446, 1380, 1308, 1287, 1234, 1099. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.7 (m, 2H, CH_2), 4.05 (m, 2H, CH_2), 6.13 (br s, 1H, NH), 7.05 (m, 1H, aromat.) 7.3 (m, 1H, aromat.), 7.65 (d, 2H, aromat.), 8.74 (s, 1H, aromat.). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 45.79, 54.57, 118.46, 121.64, 122.59, 123.79, 128.67, 150.23, 157.18. According to the above procedure were obtained compounds **3a**—**d**. Physicochemical and spectroscopic data of these compounds were in agreement with those described in ref. 14.

X-Ray Structure Determination The data were collected on a KumaCCD diffractometer using graphite monochromatized Mo$K\alpha$ (radiation with detector distance of 6 cm. More than hemisphere of reciprocal space was covered by a combination of four sets of exposures; each set had a different φ-angle (0, 90, 180, 270) and each exposure of 30 s covered 0.75 (in ω. Coverage of the unique set is over 99% complete. The collected data were reduced using the program KM4RED.[24] The structure was solved by direct methods with the program SHELXS-97[25] and refined by full-matrix least-squares method on F^2 with SHELXL-97.[26] Hydrogen atoms have been located on ΔF maps and refined with isotropic displacement parameters.

Crystal Data for **3e**: $C_{10}H_{10}N_4$, orthorhombic, *Pca*2$_1$, a=11.899 (2) Å, b=7.980 (2) Å, c=9.681 (2) Å, V=919.2 (3) Å^3, Z=4, D_x=1.346 g cm^{-3}, μ=0.087 mm^{-1}. The structure was refined on 858 reflections; 168 refined parameters; R_1=0.0334, wR_2=0.0816, GOF=1.048 for 818 reflections with $F>4\sigma(F)$ [R_1=0.0354, wR_2=0.0835 for all 858 independent reflections].

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