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# Reduction of Different Electron-Poor *N*-Heteroarylhydrazines in Strong Basic Conditions

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*In memory of Lucía*

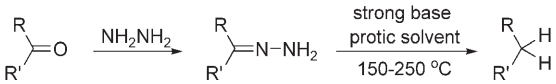
**Abstract:** The first application of the Wolff–Kishner reduction methodology to electron-poor heteroaromatic compounds is reported. Hydrazino-containing heterocycles with hydrazone-type tautomery have been reduced under basic conditions. This novel chemistry was successfully applied to mono-dehalogenate a number of electron-poor heterocycles in a regioselective manner. According to the experimental results, this reductive process is a base-catalyzed reaction that takes only place in the presence of air, probably through an oxygen-assisted mechanism. As consequence of the specific features of this kind of hydrazone/enehydrazine tautomers, the overall outcome of the process is the synthesis of a Shapiro-type reduction product by simply using a milder version of the Huang–Minlon methodology.

**Keywords:** heterocycles · hydrazone-type tautomery · hydrodehalogenation · reaction mechanisms · regioselectivity

## Introduction

The reduction of chloroarenes has been studied under a variety of conditions including free radical, catalytic and transfer hydrogenation, oxidative, and metal-catalyzed hydride delivery.[1] In particular, the hydrodehalogenation of electron-poor heteroaromatic compounds is usually achieved by catalytic hydrogenolysis and metal catalysis.[1a,d,e,2] However, these methods do not distinguish between different halogenated positions, giving rise to completely dechlorinated aromatic compounds with a few exceptions.[1d]

Hydrazine is widely used as a reagent in synthetic organic chemistry[3] but is probably most frequently associated with the transformation of carbonyl-containing compounds to the corresponding hydrazones as intermediates in the Wolff–Kishner-type reduction (Scheme 1).[4]




Scheme 1. The Huang–Minlon methodology of the Wolff–Kishner reduction.[4c,d]

Although this reaction is well known, it has never been used before for the reduction of chloro-containing heterocycles. In a few reports hydrazine was used as one of the reactants to reduce halogenated aromatic compounds.[5,6] However, oxidative agents[5] or palladium catalysts,[6] instead of basic conditions, were used to complete the hydrodehalogenations.

By chance,[7] we observed that applying different alkoxides to 2-chloro-3-hydrazino-5-azaquinoxaline (**2**) (Scheme 2) led not only to the substitution of the chloro ligand in the 2-carbon position, but also to the reduction of the hydrazine group. The resulting structures **3a–f** were confirmed by NMR spectroscopy and mass spectrometric analy-

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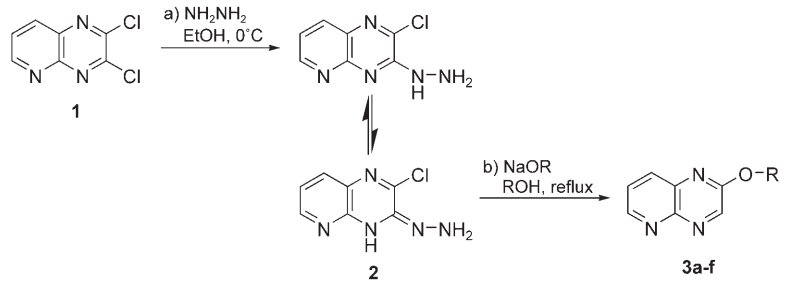



Scheme 2. Unexpected reduction of the hydrazine group of compound **2**.

sis. Additionally, the molecular structure of compound **3d** was assigned by X-ray crystallography, which verified the reduced position (Figure 1).

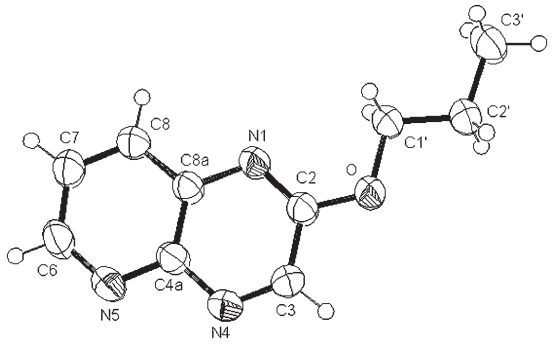



Figure 1. Molecular structure of **3d** (ORTEP diagram).

Initially, we assumed this reduction should follow the Wolff–Kishner-type mechanism from the hydrazone-type tautomer of compound **2** (Scheme 2). However, much milder conditions and shorter reaction time than even those used in the Huang–Minlon modification[4c] were required. Also, the C3 position of the resulting compound was reduced to an aromatic methine, a Shapiro[8] and Bamford–Stevens[8,9] reduction product (Scheme 3), instead of a methylene. These questions together with some references,[10] which described the decomposition of *N*-heteroaryl-*N*′-tosylhydrazines in basic conditions without studying the mechanism in depth, stimulated our interest in the reaction mechanism.

From a synthetic point of view, the applicability of this new process was very promising due to the advantages of using a two-step procedure: i) nucleophilic aromatic substitution ($S_NAr$) of the more electrophilic halogenated position with hydrazine, and ii) exclusive reduction of the substituted position using basic conditions. This new synthetic pathway could permit the dechlorination of electron-poor nitrogen-containing heterocycles without the drawbacks that previous strategies have presented, such as the lack of regioselectivity and the use of toxic and expensive catalysts. Thus, further studies were carried out.

**Abstract in Spanish:** *Se presenta la primera aplicación de la metodología usada en la reducción de Wolff-Kishner para compuestos heteroaromáticos π-deficientes. Mediante el empleo de medio básico fuerte se ha conseguido la reducción del grupo hidrazino de distintos compuestos heterocíclicos con una característica común: la presencia de un tautómero hidrazona. Este comportamiento nunca antes descrito se ha aplicado satisfactoriamente en la deshalogenación independiente y regioselectiva de distintas posiciones halogenadas de compuestos heterocíclicos π-deficientes. De acuerdo con los datos experimentales presentados, este proceso reductivo se cataliza por medio de bases fuertes y únicamente tiene lugar en sistemas abiertos, a través de un mecanismo en el que probablemente interviene el oxígeno del aire. Debido a las especiales características de esta clase de tautómeros enehidracino/hidrazónicos, el resultado global del proceso es la síntesis del producto que se obtendría a través de la reducción de Shapiro usando, simplemente, una versión más suave de la modificación de Huang-Minlon.*

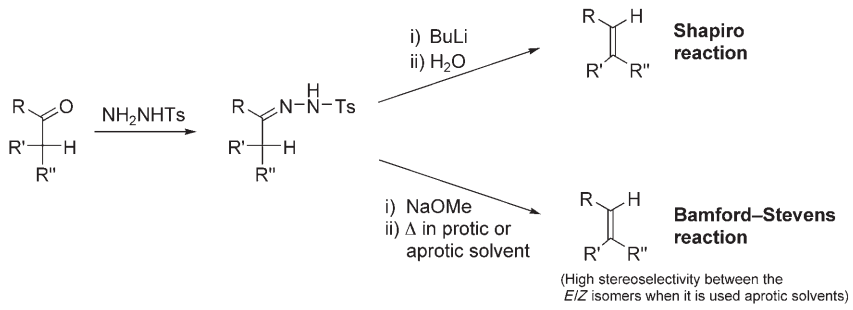
## Results and Discussion

**Regioselective synthesis of both 2- and 3-alkoxypyrido[2,3-*b*]pyrazines from 2,3-dichloropyrido[2,3-*b*]pyrazine 1**:[11] The reduction was driven by the nucleophilic attack of hydrazine monohydrate to the more electrophilic position of 2,3-dichloropyrido[2,3-*b*]pyrazine (**1**; Scheme 4). The pyrido-ring nitrogen atom dictates the regiochemistry of the reaction, inducing a different electrophilicity between the 2- and the 3-carbon positions of the compound **1**. The heterocycle **2**, which presents a hydrazone-type tautomer, was then reduced under basic conditions using either alkoxides or sodium hydroxide. The different alkoxides were prepared in situ by using the corresponding alcohols and sodium hydride before being added to a solution of compound **2** in the same alcohol.

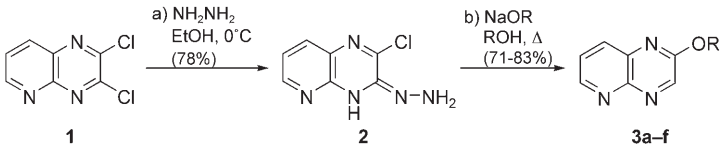
Primary alkoxides and sodium hydroxide behaved as a strong base for the reduction of the 3-carbon position and as a nucleophile for the $S_NAr$ of the chloro at the 2-carbon position, to give rise to the 2-alkoxy derivatives **3a–f** in good overall yields (71–83 %).[12] Nucleophilic substitutions occurred regardless of the temperature at which the reactions were carried out.[13]

However, when sodium isopropoxide in 2-propanol (secondary alkoxide) and potassium *tert*-butoxide (tertiary alkoxide) in *tert*-butyl alcohol were tested as reagents, the corresponding reactions did not provide the expected compounds in good yields.




Scheme 3. General Shapiro and Bamford–Stevens reduction.[8,9]




Scheme 4. Synthesis of 2-alkoxypyrido[2,3-*b*]pyrazines **3a–f** (**3a** R = H; **3b** R = Me; **3c** R = Et; **3d** R = Pr; **3e** R = Allyl; **3f** R = Benzyl). Reagents and conditions: a) $NH_2NH_2{\cdot}H_2O$ (2 equiv), EtOH, 0 °C, 1 h, 78 %; b) HNa (60 % in mineral oil, 6 equiv), ROH, 60–120 °C, 2–30 min, 71–83 %.

To exploit the potential of this methodology, the 3-alkoxy isomers **6a–c** were synthesized (Scheme 5). The dichloro compound **1** was first mono-substituted by alkoxides and then reduced following the above methodology. Compound **1** was dissolved in the appropriate alcohol and treated with sodium hydrogen carbonate to selectively give rise to 2-chloro-3-alkoxy-pyrido[2,3-*b*]pyrazines **4a–c**. Following treatment with hydrazine, which led to the formation of hydrazones **5a–c**, reductions were achieved by using basic conditions to obtain the 3-alkoxy derivatives **6a–c** in excellent overall yields (89–94 %).

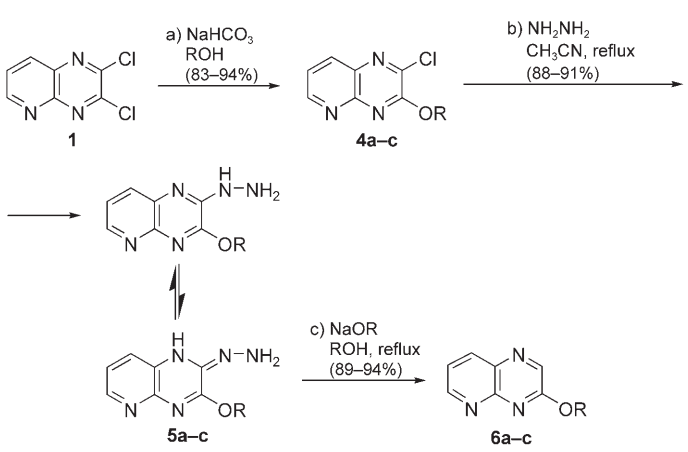
To identify the best base for the reductive step, compound **5a** (R = Me) was treated with a variety of bases in different solvents (Table 1). Sodium carbonate was not basic enough to accomplish the reaction, whereas sodium methoxide in methanol produced the fastest reduction. The use of sodium methoxide in non-protic solvents did not allow the reductive process. The final compounds **7a,b**, which contain a deuterium atom at the 2-carbon position,

Table 1. Influence of bases for the compound **5a** (1 mmol) reduction.

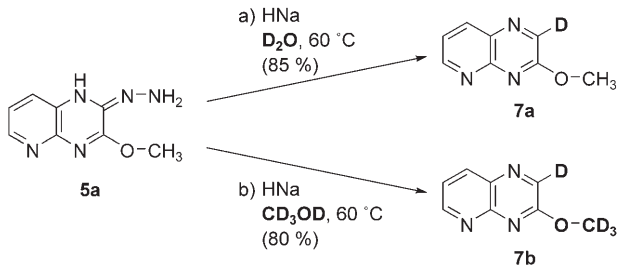
| Base | Solvent (40 mL) | Product | Yield [%][a] | Time[b] (2 equiv) | Time[b] (6 equiv) |
|---|---|---|---|---|---|
| $Na_2CO_3$ | $H_2O$ | – | – | – | – |
| NaOH | $H_2O$ | **6a** | 88–90 | >2 h | ~20 min |
| NaOD | $D_2O$ | **7a** | 85–88 | >2 h | ~30 min |
| NaOMe | MeOH | **6a** | 82–84 | 15–20 min | 1–2 min |
| NaOMe | THF | – | – | – | – |
| NaOMe | dioxane | – | – | – | – |
| $NaOCD_3$ | $CD_3OD$ | **7b** | 80–82 | ~30 min | ~5 min |
| NaOEt | EtOH | **6b** | 76–81 | 30–40 min | 2–3 min |
| NaO*i*Pr | *i*PrOH | **6c** | 74–80 | >2 h | ~10 min |
| KO*t*Bu | *t*BuOH | **6a** | 71–75 | >2 h | ~15 min |

[a] Yield of isolated product after column chromatography. [b] All the reactions were performed by stirring (500 rpm) at room temperature (~25 °C) using 2 and 6 equivalents of base. The reaction times are not optimized.

were obtained by using deuterated solvents (Scheme 6). Surprisingly, sodium [$D_3$]methoxide caused the methoxy group at the 3-carbon position to be substituted by a [$D_3$]methoxy




Scheme 5. Synthesis of 3-alkoxypyrido[2,3-*b*]pyrazines **6a–c** (**6a** R = Me; **6b** R = Et; **6c** R = *i*Pr). Reagents and conditions: a) $NaHCO_3$ (1.1 equiv), ROH, 30 min at room temperature, then 60–78 °C for 1–2 h, 83–94 %; b) $NH_2NH_2{\cdot}H_2O$ (2 equiv), acetonitrile, reflux temperature, 1 h, 88–91 %; c) HNa (60 % in mineral oil, 6 equiv), ROH, reflux temperature, 5 min, 89–94 %.



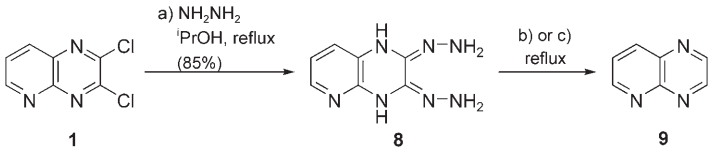

Scheme 6. Synthesis of the deuterated derivatives **7a,b**. Reagents and conditions: a) HNa (60 % in mineral oil, 6 equiv), $D_2O$, 60 °C, 30 min, 85 %; b) HNa (60 % in mineral oil, 6 equiv), $CD_3OD$, 60 °C, 5 min, 80 %.

moiety. Using sodium ethoxide and sodium isopropoxide gave rise to the same $S_NAr$ reaction, but neither potassium *tert*-butoxide nor sodium hydroxide could affect this substitution. It is, thus, clear that the primary and secondary alkoxides can generate undesired products due to their higher nucleophilicity.

Complete dehalogenation of 2,3-dichloropyrido[2,3-*b*]pyrazine (**1**) could be achieved by refluxing with an excess of

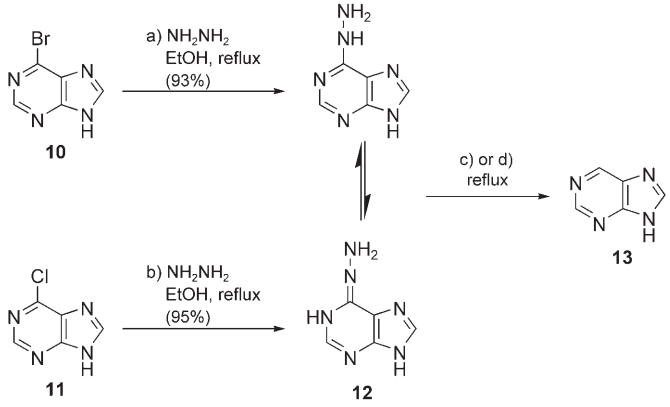
  

hydrazine monohydrate in 2-propanol followed by addition of a base (Scheme 7).




Scheme 7. Synthesis of 5-azaquinoxaline **9**. Reagents and conditions: a) $NH_2NH_2{\cdot}H_2O$ (6 equiv), *i*PrOH, reflux temperature, 3 h, 85%; b) NaOH (6 equiv), $H_2O$, reflux temperature, 25 min, 94%; c) HNa (60% in mineral oil, 6 equiv), MeOH, reflux temperature, 10 min, 91%.

**Reduction of the 6-carbon position of several halogenated purines**: With the aim of establishing the full potential of this methodology, other halogenated heterocycles were tested. Both 6-bromo- and 6-chloropurine were reduced by using the same synthetic pathway as was previously mentioned (Scheme 8). Compound **12** was obtained from both

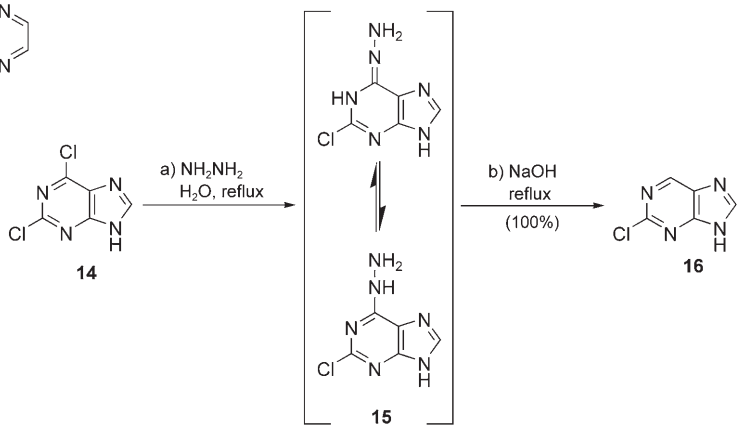



Scheme 8. Synthesis of purine **13**. Reagents and conditions: a) $NH_2NH_2{\cdot}H_2O$ (2 equiv), EtOH, reflux temperature, 30 min, 93%; b) $NH_2NH_2{\cdot}H_2O$ (2 equiv), EtOH, reflux temperature, 2 h, 95%; c) NaOH (6 equiv), $H_2O$, reflux, 12 h, 100%; d) HNa (60% in mineral oil, 6 equiv), MeOH, reflux, 8 h, 67%.

starting materials through reaction with hydrazine and reduced into purine **13** by using basic conditions. This heterocyclic system is less prone to undergoing $S_NAr$ reactions than the azaquinoxaline ring, and thus longer times for both the substitution and reduction steps were required. Consequently, a direct relationship between the electrophilic character of the ring and the ease of reducing the hydrazone group was apparent.

At this stage of our research we investigated more challenging applications. We were attracted by the difficult regioselective reduction of 2,6-dichloropurine into 2-chloropurine, an interesting non-commercially available synthon in medicinal chemistry. In the only report of this reduction, use of aqueous sodium acetate and 10% Pd/charcoal under a hydrogen atmosphere gave 2-chloropurine in 40% yield.[14]

By employing the single-pot procedure shown in Scheme 9, in which water, hydrazine, and sodium hydroxide were used as the only reagents and solvents, the pure final product **16** was obtained in quantitative yield.[15]

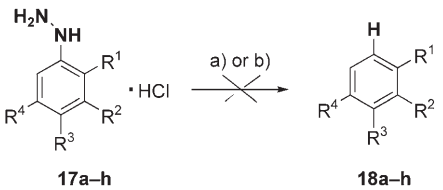



Scheme 9. Regioselective synthesis of 2-chloropurine **16**. Reagents and conditions: a) $NH_2NH_2{\cdot}H_2O$ (2 equiv), $H_2O$, reflux temperature, 30 min; b) NaOH (12 equiv), reflux temperature, 3.5 h, 100% two steps.

The regioselective reduction is favored by the low electrophilicity of the 2-carbon position of the purine ring, which avoids the feasible nucleophilic substitution in spite of the basic conditions. Notably, when sodium hydroxide was utilized, the yield was much better than when sodium methoxide was used.

**Behavior of several *N*-phenylhydrazines under strong basic conditions**: Up until this point we had studied the reduction of *N*-heteroarylhydrazines with hydrazone-type tautomery. With the aim of understanding the mechanism of the reduction process, a set of *N*-phenylhydrazines was tested under the same reduction conditions to determine the importance of the pyridine-type nitrogen presence.

As expected, under the same basic conditions none of the phenyl derivatives were reduced even though reaction times were increased (Scheme 10). The lack of reactivity of these *N*-phenylhydrazines confirms the requirement of an endocy-

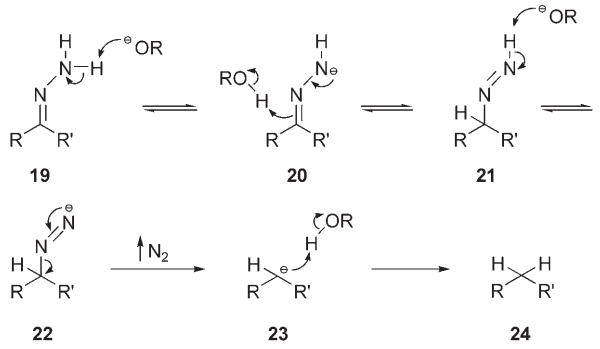



Scheme 10. Non-reaction of a set of *N*-phenylhydrazines under strong basic conditions. (**17a** $R^1$=Cl, $R^2$=$R^3$=$R^4$=H; **17b** $R^2$=Cl, $R^1$=$R^3$=$R^4$=H; **17c** $R^3$=Cl, $R^1$=$R^2$=$R^4$=H; **17d** $R^2$=Br, $R^1$=$R^3$=$R^4$=H; **17e** $R^3$=Br, $R^1$=$R^2$=$R^4$=H; **17f** $R^3$=Et, $R^1$=$R^2$=$R^4$=H; **17g** $R^3$=OMe, $R^1$=$R^2$=$R^4$=H; **17h** $R^2$=$R^4$=$NO_2$, $R^1$=$R^3$=H). Reagents and conditions: a) NaOH (6 equiv), $H_2O$, reflux temperature, 24 h; b) HNa (60% in mineral oil, 6 equiv), MeOH, reflux temperature, 24 h.

clic nitrogen atom in the α-position relative to the carbon atom attached to the hydrazine/hydrazone group.

**Mechanistic aspects of the novel reaction**: The Wolff–Kishner-type reduction mechanism has been studied for almost a century.[4,16] It is accepted that the reaction begins with the tautomerization of hydrazone **19** into its alkyl diimide **21** form (Scheme 11) mediated by basic conditions.[4d,16] The




Scheme 11. The Wolff–Kishner reduction mechanism.

demonstration by Szmant et al.[16b] that this reaction is first order with respect to base concentration led to a mechanistic proposal[16c–g] that is now largely reproduced in every organic chemistry textbook.

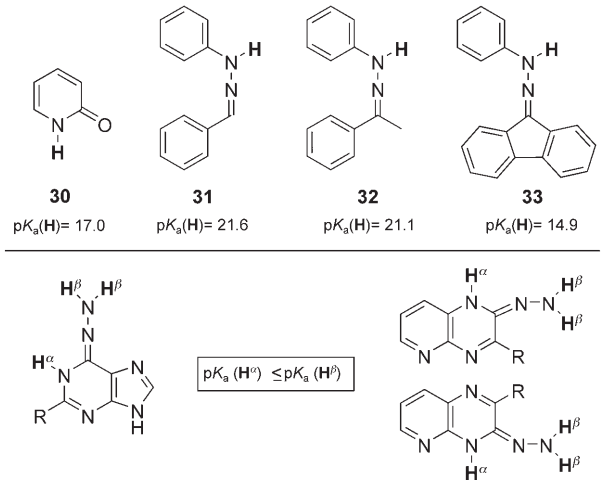
The novel reduction presented within this article has the same kinetic features as the Wolff–Kishner-type reduction, despite the new method needing much milder conditions to be achieved. The catalytic role of the base in *N*-heteroarylhydrazine reductions was verified in all the samples shown in this work by using less than one equivalent of base (except in those where it was also produced a $S_NAr$, in which less than two equivalents of base was used). The experimental results demonstrated that, as in the Wolff–Kishner reduction, reaction kinetics are undoubtedly influenced by the concentration of base. The reaction rate of the synthesis of 2-chloropurine **16** was the most influenced by the base concentration. In addition, after this reaction was completed, the neutralization of the resulting mixture disclosed no base was consumed during the reaction.

Although the kinetic features of the hydrazino-containing heterocycle reduction are comparable to that of the Wolff-Kishner reaction, the resulting product is the one expected when using the Shapiro or the Bamford–Stevens methodology. Therefore, if the reduction took place by the Wolff–Kishner mechanism, the non-aromatic *dihydroheteroaryl* intermediate produced through this mechanism should be subsequently oxidized by the oxygen present in the air. For this reason the reaction was realized in absence of air to disclose the importance of the oxygen in the synthetic process.

When the reactions were carried out under nitrogen atmosphere in degasified solvent,[17] the synthesis of the final products was not achieved. Although these experiments confirmed the implication of the oxygen in the process, it was not possible to isolate the *dihydroheteroaryl* intermediate in any of the samples.[18] Consequently, other alternative mechanisms were considered.

Despite the fact that the Bamford–Stevens reaction is achieved in milder conditions than the Shapiro one, its mechanism was ruled out as it was confirmed that the reduction of hydrazine-containing heterocycles could only be achieved in the presence of protic solvents. Moreover, to accomplish the Bamford–Stevens reaction it is essential a good leaving group, like the tosyl group, is attached to the hydrazone.[8,9,19]

Although the Shapiro reduction also requires a good leaving group attached to the hydrazone, the special acidic properties of this kind of compounds allow an oxygen-assisted variant of this mechanism to be considered as a possible alternative. The acidity measurements in DMSO reported by Bordwell et al. for the N–H groups of 2-pyridone **30** ($pK_a$ = 17.0)[20] and of some hydrazones (acetophenone phenylhydrazone **31**, $pK_a$ = 21.6, benzaldehyde phenylhydrazone **32**, $pK_a$ = 21.1 and 9-fluorenone phenylhydrazone **33**, $pK_a$ = 14.9)[21] are evidence for regarding that the endocyclic N–H of the hydrazone-tautomer derivatives presented in this work[22] must have similar acidic properties, if not higher, than the hydrazone amine group (Scheme 12).

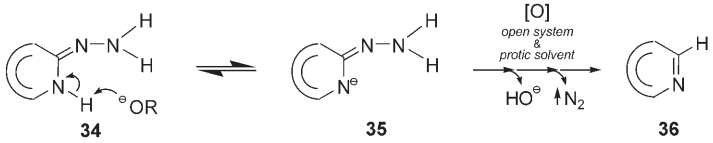



Scheme 12. Comparison among the acidity measurements in DMSO of several related compounds.

However, it was not possible to isolate any *heteroaryldiazene* intermediate[23] of the compounds presented in this article. Hence, although we propose that the mechanism whereby the reduction of these compounds occurs must start with the abstraction of the endocyclic N–H proton of the hydrazone-type tautomer **34** (Scheme 13), there are not enough experimental data to conclude a reliable mechanistic proposal.

So far four empirically verified facts disclose the main reaction requirements: 1) the base has a catalytic role; 2) only *N*-heteroarylhydrazines with a hydrazone-type tautomery are reduced under basic conditions; 3) the use of protic sol-




Scheme 13. Preliminary proposal for mechanism.

vents is indispensable for achieving the reduction; and 4) the synthetic process is only effective in the presence of air. Therefore, at this early stage of the research it is expedient to suggest just a simple preliminary proposal (Scheme 13) supported by the confirmed requirements of the overall process.

## Conclusions and Outlook

In conclusion, a new application of the Wolff–Kishner reduction methodology has been achieved. For the first time, hydrazino-containing heterocycles with a hydrazone-type tautomery have been reduced under basic conditions. A new way to monodehalogenate electron-poor heterocycles in a regioselective manner has been provided. This simple two-step procedure is metal-free, inexpensive, highly efficient, and displays low-toxicity. In addition, this strategy has been proven to selectively generate different isomers from the same building block and consequently it could be used as a valuable tool to obtain diversity in small-molecule compound library synthesis.[24]

According to the experimental results shown within this paper, the reduction of electron-poor *N*-heteroarylhydrazines is a base-catalyzed reaction that takes only place in the presence of air, probably through an oxygen-assisted mechanism. As a consequence of the specific features of this kind of hydrazone/enehydrazine tautomers, the overall outcome of the process is the synthesis of a Shapiro-type reduction product by simply using a milder version of the Huang–Minlon methodology. Further investigations on the study of the full mechanism involved in this reaction are ongoing in our laboratory.

Nevertheless, one of the most promising features of this reaction is the reactivity inversion of the reduced carbon atom. Through the simple and mild methodology used for this novel reduction, the most electrophilic position of an electron-poor heterocycle is transformed into a position with nucleophilic character. Therefore, the presented research work could be only the first step in the applications of this reaction mechanism.

## Experimental Section

**General methods**: All reactions were monitored by thin-layer chromatography (TLC) carried out on precoated aluminum sheets by using UV light as a visualizing agent. Flash chromatography was performed with 230–240 mesh silica gel, and the solvent mixture in brackets was used as eluent. Evaporations were carried out in vacuo in a rotary evaporator. Melting points (m.p.) were determined in open capillaries on a melting point apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$, [$D_6$]DMSO, [$D_6$]acetone or $CD_3CN$ solutions on a 300.13 MHz $^1H$ NMR spectrometer and a 75.58 MHz $^{13}C$ NMR spectrometer, and chemical shifts (ppm) are reported relative to the solvent peak. Signals are designated as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quadruplet; sp, septuplet; m, multiplet. Coupling constants ($J$) are expressed in Hertz. All the solids were recrystallized from water before elemental analyses were carried out. HPLC analyses were carried out in analytical instrument equipped with a UV detector. Eluents used were analytical grade. Mass spectra were obtained by Electron Impact at 70 eV on low (MS (EI)) and high (HRMS (EI)) resolution mass spectrometers.

**Procedure for the preparation of 2,3-dichloropyrido[2,3-*b*]pyrazine (1)**: Compound **1** was prepared from commercially available 2,3-diaminopyridine as previously described.[11]

**Procedure for the preparation of 2-chloro-3-hydrazinopyrido[2,3-*b*]pyrazine (2)**: A solution of hydrazine monohydrate (0.116 mL, 2 mmol) in ethanol (5 mL) was added dropwise to a cooled solution of **1** (0.2 g, 1 mmol) in ethanol (10 mL) at 0 C. The mixture was stirred for 1 h. The resulting precipitate was filtered and washed with ethanol (10 mL), $CH_2Cl_2$ (10 mL), and diethyl ether (10 mL). Compound **2** was obtained as a yellow solid (78%); m.p. >300°C; $^1H$ NMR (300 MHz, $CD_3CN$): $\delta$ = 8.90–8.81 (m, 1H), 8.22–8.15 (m, 1H), 7.73 (bs, 1H), 7.49–7.42 (m, 1H), 4.48 ppm (bs, 2H); HRMS (EI): calcd for $C_7H_6N_5Cl$ ($[M]^+$ 195.031173, found 195.031275 (deviation −0.5 ppm).

**Procedures for the preparation of the reduced and substituted derivatives 3a–f**

**1*H*-Pyrido[2,3-*b*]pyrazin-2-one (3a)**: Sodium hydroxide (0.24 g, 6 mmol) was added to water (20 mL) and the suspension was stirred at room temperature until complete dissolution. Then the hydrazino derivative **2** (195.6 mg, 1 mmol) was added, and the resulting mixture was stirred at 60°C for 15 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:1). Compound **3a** was obtained as a light brown solid (81%); m.p. >300°C; $R_f$ = 0.15 (hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, [$D_6$]DMSO): $\delta$ = 12. 60 (bs, 1H), 8.58 (dd, $^3J$(H,H) = 4.4 Hz, $^3J$(H,H) = 1.7 Hz, 1H), 8.42 (s, 1H), 7.78 (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 1.7 Hz, 1H), 7.63 ppm (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 4.4 Hz, 1H); $^{13}C$ NMR (75 MHz, [$D_6$]DMSO): $\delta$ = 155.1 (CH), 154.3, 144.8 (CH), 142.7, 127.7, 125.4 (CH), 124.6 ppm (CH); HRMS (EI): calcd for $C_7H_5N_3O$ ($[M]^+$) 147.043262, found 147.042967 (deviation 2.0 ppm); elemental analysis calcd (%) for $C_7H_5N_3O$: C 57.14, H 3.64, N 28.56; found: C 57.42, H 3.80, N 28.34.

**2-Methoxypyrido[2,3-*b*]pyrazine (3b)**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to methanol (20 mL), and the mixture was stirred for 10 min at room temperature. Then the hydrazino derivative **2** (195.6 mg, 1 mmol) was added and the resulting mixture was stirred at 60°C for 2 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 2:3). Compound **3b** was obtained as a white solid (71%); m.p. 70–72°C; $R_f$ = 0.27 (hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.92 (dd, $^3J$(H,H) = 4.3 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 8.65 (s, 1H), 8.19 (dd, $^3J$(H,H) = 8.3 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 7.60 (dd, $^3J$(H,H) = 8.3 Hz, $^3J$(H,H) = 4.3 Hz, 1H), 4.10 ppm (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 158.0, 149.9 (CH), 148.8, 142.9 (CH), 136.3 (CH), 135.7, 125.3 (CH), 54.3 ppm ($CH_3$); HRMS (EI): Calcd for $C_8H_7N_3O$ ($[M]^+$) 161.058912, found 161.058601 (deviation 1.9 ppm); elemental analysis calcd (%) for $C_8H_7N_3O$: C 59.62, H 4.38, N 26.07; found: C 59.44, H 4.60, N 25.88.

**2-Ethoxypyrido[2,3-*b*]pyrazine (3c)**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to ethanol (20 mL), and the mixture was stirred for 10 min at room temperature. Then the hydrazino derivative **2** (195.6 mg, 1 mmol) was added and the resulting mixture was stirred at 60°C for 10 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 2:3). Compound **3c** was obtained as a light yellow solid (83%); m.p. 67–69°C; $R_f$ = 0.35 (Hexanes/EtOAc 1:2); $^1H$ NMR

(300 MHz, $CDCl_3$): $\delta = 8.92$ (dd, $^3J(H,H) = 4.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 8.63 (s, 1H), 8.16 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 7.59 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 4.3$ Hz, 1H), 4.53 (q, $^3J(H,H) = 7.1$ Hz, 2H), 1.47 ppm (t, $^3J(H,H) = 7.1$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta =$ 157.7, 149.8 (CH), 148.6, 143.1 (CH), 136.2 (CH), 135.7, 125.2 (CH), 63.1 ($CH_2$), 14.3 ppm ($CH_3$); HRMS (EI): calcd for $C_9H_9N_3O$ ($[M]^+$) 175.074562, found 175.074155 (deviation 2.3 ppm); elemental analysis calcd (%) for $C_9H_9N_3O$: C 61.70, H 5.18, N 23.99; found: C 61.64, H 5.40, N 23.66.

**2-Propoxypyrido[2,3-*b*]pyrazine (3d)**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to propanol (20 mL), and the mixture was stirred for 10 min at room temperature. Then the hydrazino derivative **2** (195.6 mg, 1 mmol) was added, and the resulting mixture was stirred at 60°C for 15 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:3). Compound **3d** was obtained as a light brown solid (74%); m.p. 75–78°C; $R_f = 0.4$ (Hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.90$ (dd, $^3J(H,H) = 4.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 8.64 (s, 1H), 8.15 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 7.59 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 4.3$ Hz, 1H), 4.42 (t, $^3J(H,H) = 6.7$ Hz, 2H), 1.93–1.81 (m, 2H), 1.05 ppm (t, $^3J(H,H) = 7.4$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 157.9$, 149.7 (CH), 148.7, 143.1 (CH), 136.2 (CH), 135.7, 125.2 (CH), 68.8 ($CH_2$), 22.1 ($CH_2$), 10.5 ppm ($CH_3$); HRMS (EI): Calcd for $C_{10}H_{11}N_3O$ ($[M]^+$) 189. 090212, found 189.089995 (deviation 1.2 ppm); elemental analysis calcd (%) for $C_{10}H_{11}N_3O$: C 63.48, H 5.86, N 22.21; found: C 63.10, H 5.99, N 22.02.

**2-Allyloxypyrido[2,3-*b*]pyrazine (3e)**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to allyl alcohol (20 mL), and the mixture was stirred for 10 min at room temperature. Then the hydrazino derivative **2** (195.6 mg, 1 mmol) was added and the resulting mixture was stirred at 60°C for 15 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:3). Compound **3e** was obtained as a light brown solid (77%); m.p. 72–73°C; $R_f = 0.4$ (hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.83$ (dd, $^3J(H,H) = 4.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 8.68 (s, 1H), 8.17 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 7.60 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 4.3$ Hz, 1H), 6.19–6.06 (m, 1H), 5.51–5.44 (m, 1H), 5.36–5.31 (m, 1H), 5.01–4.98 ppm (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 156.4$, 148.6 (CH), 143.9, 143.7, 138.9, 137.6 (CH), 130.7, 123.8 (CH), 10.3 (CH), 8.3 ppm (CH); HRMS (EI): calcd for $C_{10}H_9N_3O$ ($[M]^+$) 187.074562, found 187.074828 (deviation −1.4 ppm); elemental analysis calcd (%) for $C_{10}H_9N_3O$: C 64.16, H 4.85; N 22.45; found: C 64.00, H 5.16, N 22.11.

**2-Benzyloxypyrido[2,3-*b*]pyrazine (3f)**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to benzylic alcohol (20 mL), and the mixture was stirred for 30 min at room temperature. Then the hydrazino derivative **2** (195.6 mg, 1 mmol) was added, and the resulting mixture was stirred at 120°C for 60 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:3). Compound **3f** was obtained as a light brown solid (71%); m.p. 67–69°C; $R_f = 0.5$ (Hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.94$ (dd, $^3J(H,H) = 4.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 8.71 (s, 1H), 8.21 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H), 7.62 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 4.3$ Hz, 1H), 7.53–7.49 (m, 2H), 7.43–7.33 (m, 3H), 5.54 ppm (s, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 157.4$, 150.1 (CH), 148.8, 142.9 (CH), 136.3 (CH), 135.8, 135.6, 128.7 (CH), 128.6 (CH), 128.5 (CH), 125.4 (CH), 68.9 ppm ($CH_2$); HRMS (EI): calcd for $C_{14}H_{11}N_3O$ ($[M]^+$) 237.090212, found 237.089768 (deviation 1.9 ppm); elemental analysis calcd (%) for $C_{14}H_{11}N_3O$: C 70.87, H 4.67, N 17.71; found: C 71.04, H 4.43, N 17.88.

**Procedures for the preparation of the 3-alkoxy-2-chloro derivatives 4a–c**

**2-Chloro-3-methoxypyrido[2,3-*b*]pyrazine (4a)**: Sodium hydrogen carbonate (92 mg, 1.1 mmol) was added to a stirred solution of compound **1** (200 mg, 1 mmol) in methanol (10 mL) cooled at 0°C. The mixture was stirred for 30 min at room temperature and then 1 h at 60°C. Then the solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:4). Compound **5a** was obtained as a white solid (83%); m.p. 130–132°C; $R_f = 0.55$ (hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.97$ (dd, $^3J(H,H) = 4.4$ Hz, $^3J(H,H) =$ 1.9 Hz, 1H), 8.28 (dd, $^3J(H,H) = 8.2$ Hz, $^3J(H,H) = 1.9$ Hz, 1H), 7.55 (dd, $^3J(H,H) = 8.2$ Hz, $^3J(H,H) = 4.4$ Hz, 1H), 4.25 ppm (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 156.0$, 153.3 (CH), 149.3, 140.7, 136.9 (CH), 133.2, 123.1 (CH), 55.9 ppm ($CH_3$); HRMS (EI): calcd for $C_8H_6N_3OCl$ ($[M]^+$) 195.019940, found 195.019663 (deviation 1.4 ppm).

**2-Chloro-3-ethoxypyrido[2,3-*b*]pyrazine (4b)**: Sodium hydrogen carbonate (92 mg, 1.1 mmol) was added to a stirred solution of compound **1** (200 mg, 1 mmol) in ethanol (10 mL) at room temperature. The mixture was stirred for 2 h at reflux temperature. Then the solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:5). Compound **4b** was obtained as a white solid (94%); m.p. 128–130°C; $R_f = 0.58$ (Hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.97$ (dd, $^3J(H,H) = 4.4$ Hz, $^3J(H,H) = 1.9$ Hz, 1H), 8.28 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 1.9$ Hz, 1H), 7.55 (dd, $^3J(H,H) = 8.3$ Hz, $^3J$-$(H,H) = 4.4$ Hz, 1H), 4.72 (q, $^3J(H,H) = 7.1$ Hz, 2H), 1.54 ppm (t, $^3J$-$(H,H) = 7.1$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 155.7$, 153.2 (CH), 151.7, 141.0, 136.9 (CH), 133.1, 123.0 (CH), 65.0 ($CH_2$), 14.3 Hz ($CH_3$); MS (EI): $m/z$: 209 ($[M]^+$); 211 ($[M+2]$).

**2-Chloro-3-isopropoxypyrido[2,3-*b*]pyrazine (4c)**: Sodium hydrogen carbonate (92 mg, 1.1 mmol) was added to a stirred solution of compound **1** (200 mg, 1 mmol) in 2-propanol (10 mL) at room temperature. The mixture was stirred for 4 h at reflux temperature. Then the solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 1:5). Compound **4c** was obtained as a white solid (94%); m.p. 108–111°C; $R_f = 0.62$ (hexanes/EtOAc 1:2); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.97$ (dd, $^3J(H,H) = 4.4$ Hz, $^3J(H,H) = 1.9$ Hz, 1H), 8.28 (dd, $^3J(H,H) = 8.3$ Hz, $^3J(H,H) = 1.9$ Hz, 1H), 7.55 (dd, $^3J(H,H) =$ 8.3 Hz, $^3J(H,H) = 4.4$ Hz, 1H), 4.72 (q, $^3J(H,H) = 7.1$ Hz, 2H), 1.54 (t, $^3J$-$(H,H) = 7.1$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 155.7$, 153.2 (CH), 151.7, 141.0, 136.9 (CH), 133.1, 123.0 (CH), 65.0 ($CH_2$), 14.3 ppm ($CH_3$); MS (EI): $m/z$ 223 ($[M]^+$); 225 ($[M+2]$).

**Procedures for the preparation of the 3-alkoxy-2-hydrazino derivatives 5a–c**

**2-Hydrazino-3-methoxypyrido[2,3-*b*]pyrazine (5a)**: Hydrazine monohydrate (0.116 mL, 2 mmol) was added to a solution of **4a** (191 mg, 1 mmol) in acetonitrile (10 mL), and the mixture was stirred at reflux temperature for 1 h. Then the solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate). Compound **5a** was obtained as a light yellow solid (88%); m.p. 126–128°C. $^1H$ NMR (300 MHz, [D$_6$]acetone): $\delta = 8.80$ (bs, 1H), 8.57 (bs, 1H), 8.05–7.95 (m, 1H), 7.43 (bs, 1H), 4.12 (s, 3H), 2.86 ppm (s, 2H); $^{13}C$ NMR (75 MHz, $CD_3COCD_3$): $\delta = 154.9$, 146.9, 146.8 (CH), 145.2, 141.7, 134.0 (CH), 122.2 (CH), 53.9 ppm ($CH_3$); MS (EI): $m/z$: 191 ($[M]^+$).

**3-Ethoxy-2-hydrazinopyrido[2,3-*b*]pyrazine (5b)**: Hydrazine monohydrate (0.116 mL, 2 mmol) was added to a solution of **4b** (205 mg, 1 mmol) in acetonitrile (10 mL) and the mixture was stirred at reflux temperature for 1 h. Then the solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate). Compound **5b** was obtained as a light brown solid (91%); m.p. 120–126°C. $^1H$ NMR (300 MHz, $CD_3CN$): $\delta = 8.62$ (sa, 2H), 8.07 (d, $^3J(H,H) = 8.1$ Hz, 1H), 7.48 (dd, $^3J(H,H) = 8.1$ Hz, $^3J(H,H) = 4.5$ Hz, 1H), 4.69 (q, $^3J(H,H) =$ 7.0 Hz, 2H), 1.55 (t, $^3J(H,H) = 7.0$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$): $\delta = 165.3$, 155.6, 147.24 (CH), 142.2, 134.4 (CH), 134.3, 122.6 (CH), 63.9 ($CH_2$), 14.0 Hz ($CH_3$); MS (EI): $m/z$: 205 ($[M]^+$).

**3-Isopropoxy-2-hydrazinopyrido[2,3-*b*]pyrazine (5c)**: Hydrazine monohydrate (0.116 mL, 2 mmol) was added to a solution of **4c** (205 mg, 1 mmol) in acetonitrile (10 mL) and the mixture was stirred at reflux temperature for 1 h. Then the solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate). Compound **5c** was obtained as a light brown solid (87%); m.p. 110–115°C. $^1H$ NMR (300 MHz, $CD_3CN$): $\delta = 8.62$ (sa, 2H), 8.07 (d, $^3J(H,H) = 8.1$ Hz, 1H), 7.48 (dd, $^3J(H,H) = 8.1$ Hz, $^3J(H,H) = 4.5$ Hz, 1H), 4.69 (q, $^3J(H,H) =$ 7.0 Hz, 2H), 1.55 ppm (t, $^3J(H,H) = 7.0$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CD_3CN$): $\delta = 165.3$, 155.6, 147.24 (CH), 142.2, 134.4 (CH), 134.3, 122.6 (CH), 63.9 ($CH_2$), 14.0 ppm ($CH_3$); MS (EI): $m/z$: 219 ($[M]^+$).

**Procedures for the preparation of the reduced compounds 6a–c**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was

added portionwise to the adequate alcohol (20 mL) and the mixture was stirred for 10 min at room temperature. Then the corresponding hydrazino derivative (1 mmol) was added and the resulting mixture was stirred at 60 °C for 5 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 2:3).

**3-Methoxypyrido[2,3-*b*]pyrazine (6a)**: Compound **6a** was obtained as a white solid (89%); m.p. 69–71 °C; $R_f$ = 0.27 (Hexanes/EtOAc 1:2); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.99 (dd, $^3J$(H,H) = 4.4 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 8.57 (s, 1H), 8.37 (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 7.55 (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 4.4 Hz, 1H), 4.19 ppm (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 159.9, 153.2 (CH), 141.4 (CH), 137.9 (CH), 133.5, 122.2 (CH), 122.1, 14.4 ppm ($CH_3$); HRMS (EI): calcd for $C_8H_7N_3O$ ($[M]^+$) 161.058912, found 161.059078 (deviation −1.0 ppm); elemental analysis calcd (%) for $C_8H_7N_3O$: C 59.62, H 4.38, N 26.07; found: C 59.66, H 4.22, N 26.12.

**3-Ethoxypyrido[2,3-*b*]pyrazine (6b)**: Compound **6b** was obtained as a light brown solid (94%); m.p. 68–69 °C; $R_f$ = 0.35 (hexanes/EtOAc 1:2); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.97 (dd, $^3J$(H,H) = 4.3 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 8.54 (s, 1H), 8.36 (dd, $^3J$(H,H) = 8.3 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 7.52 (dd, $^3J$(H,H) = 8.3 Hz, $^3J$(H,H) = 4.3 Hz, 1H), 4.65 (q, $^3J$(H,H) = 7.1 Hz, 2H), 1.50 ppm (t, $^3J$(H,H) = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 159.9, 153.2 (CH), 141.4 (CH), 137.9 (CH), 133.5, 122.2 (CH), 122.1, 63.4 ($CH_2$), 14.4 ppm ($CH_3$); HRMS (EI): calcd for $C_9H_9N_3O$ ($[M]^+$) 175.074562, found 175.074804 (deviation −1.4 ppm); elemental analysis calcd (%) for $C_9H_9N_3O$: C 61.70, H 5.18, N 23.99; found: C 61.77, H 5.20, N 23.96.

**3-Isopropoxypyrido[2,3-*b*]pyrazine (6c)**: Compound **6c** was obtained as a light brown solid (94%); m.p. 66–67 °C; $R_f$ = 0.41 (hexanes/EtOAc 1:2); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.85 (dd, $^3J$(H,H) = 4.4 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 8.54 (s, 1H), 8.11 (dd, $^3J$(H,H) = 8.3 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 7.48 (dd, $^3J$(H,H) = 8.3 Hz, $^3J$(H,H) = 4.4 Hz, 1H), 5.44 (sp, $^3J$(H,H) = 6.2 Hz, 1H), 1.40 ppm (d, $^3J$(H,H) = 6.3 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 159.9, 153.2 (CH), 141.4 (CH), 137.9 (CH), 133.5, 122.2 (CH), 122.1, 70.8 (CH), 22.1 ppm ($CH_3$); calcd for $C_{10}H_{11}N_3O$ ($[M]^+$) 189. 090212, found 189.089972 (deviation 1.2 ppm); elemental analysis calcd (%) for $C_{10}H_{11}N_3O$: C 63.48, H 5.86, N 22.21; found: C 63.05, H 5.97, N 22.01.

**Procedures for the preparation of the deuterated compounds**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to the corresponding deuterated solvent (15 mL), and the mixture was stirred for 20 min at room temperature. Then the hydrazino derivative **5a** (0.161 mg, 1 mmol) was added and the resulting mixture was stirred at room temperature for 5–30 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 2:3).

**2-Deuterio-3-methoxypyrido[2,3-*b*]pyrazine (7a).** Compound **7a** was obtained as a light yellow solid (91%); m.p. 70–73 °C; $R_f$ = 0.25 (hexanes/EtOAc 1:2); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.92 (dd, $^3J$(H,H) = 4.4 Hz, $^3J$(H,H) = 1.9 Hz, 1H), 8.31 (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 1.9 Hz, 1H), 7.47 (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 4.4 Hz, 1H), 4.13 ppm (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 160.2, 153.5 (CH), 150.1, 140.7 (t, CH, $J$ = 115 Hz), 138.3 (CH), 133.6, 122.6, 122.7 (CH), 54.9 ppm ($CH_3$); MS (EI): $m/z$: 162.1 ($[M]^+$).

**3-([D$_3$]Methoxy)-pyrido[2,3-*b*]pyrazine-2-[D] (7b).** Compound **7b** was obtained as a white solid (81%); m.p. 67–69 °C; $R_f$ = 0.24 (hexanes/EtOAc 1:2); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.97 (bs, 1H), 8.36 (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 1.9 Hz, 1H), 7.53 ppm (dd, $^3J$(H,H) = 8.2 Hz, $^3J$(H,H) = 4.4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 160.2, 153.2 (CH), 150.1, 140.7 (t, CH, $J$ = 115 Hz), 137.9 (CH), 136.3, 133.6, 122.4 (CH), 53.9 ppm (sp, $CH_3$, $J$ = 80 Hz); MS (EI): $m/z$: 165.1 ($[M]^+$).

**Procedure for the preparation of the dihydrazino derivative 8**: Hydrazine monohydrate (0.348 mL, 6 mmol) was added to a solution of **1** (0.2 g, 1 mmol) in 2-propanol (20 mL). The mixture was stirred at room temperature for 3 h. The resulting precipitate was filtered and washed with ethanol (10 mL), $CH_2Cl_2$ (10 mL), and diethyl ether (10 mL). Compound **8** was obtained as a yellow solid (85%); m.p. >300 °C; MS (EI): $m/z$: 191.2 ($[M]^+$).

**Procedure for the preparation of pyrido[2,3-*b*]pyrazine (9)**: A dispersion of sodium hydride (60% in mineral oil, 0.24 mg, 6 mmol) or sodium hydroxide (0.24 mg, 6 mmol) was added portionwise to methanol or water (20 mL), and the mixture was stirred for 10 min at room temperature. Then the dihydrazino derivative **8** (0.191 mg, 1 mmol) was added and the resulting mixture was stirred at reflux temperature for 10–25 min. The solvent was evaporated and the crude residue was purified by flash chromatography (ethyl acetate/hexane 2:3). Compound **9** was obtained as a light brown solid (89%); m.p. 88–90 °C; $R_f$ = 0.55 (hexanes/EtOAc 1:2); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.16 (dd, $^3J$(H,H) = 4.2 Hz, $^3J$(H,H) = 1.9 Hz, 1H), 9.05 (d, $^3J$(H,H) = 1.8 Hz, 1H), 8.92 (s, 1H), 8.45 (dd, $^3J$(H,H) = 8.4 Hz, $^3J$(H,H) = 1.9 Hz, 1H), 7.71 ppm (dd, $^3J$(H,H) = 8.4 Hz, $^3J$(H,H) = 4.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 154.3 (CH), 151.4, 147.8 (CH), 146.1 (CH), 138.7 (CH), 138.5, 125.46 ppm (CH); MS (EI): $m/z$: 131.1 ($[M]^+$); elemental analysis calcd (%) for $C_7H_5N_3$: C 64.11, H 3.84, N 32.04; found: C 64.09, H 4.05, N 32.01.

**Procedures for the preparation of 6-hydrazinopurine (12)**

**From 6-bromopurine (10)**: Hydrazine monohydrate (0.116 mL, 2 mmol) was added to a solution of 6-bromopurine **10** (0.199 g, 1 mmol) in ethanol (15 mL). The mixture was stirred and heated at reflux temperature for 30 min. The resulting precipitate was filtered and washed with ethanol (10 mL), $CH_2Cl_2$ (10 mL), and diethyl ether (10 mL). Compound **12** was obtained as a white solid (93%); m.p. 246–250 °C (decomp) [lit. [25] m.p. 246–247.5 °C (decomp)].

**From 6-chloropurine (11)**: Hydrazine monohydrate (0.116 mL, 2 mmol) was added to a solution of **11** (0.154 g, 1 mmol) in ethanol (15 mL). The mixture was stirred and heated at reflux temperature for 2 h. The resulting precipitate was filtered and washed with ethanol (10 mL), $CH_2Cl_2$ (10 mL), and diethyl ether (10 mL). Compound **12** was obtained as a white solid (95%); m.p. 246–248 °C (decomp) [lit. [25] m.p. 246–247.5 °C (decomp)]; $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta$ = 12.85 (bs, 1H), 8.73 (bs, 1H), 8.17 (s, 1H), 8.08 (s, 1H), 4.62 ppm (bs, 2H); HR (LSIMS): calcd for $C_5H_6N_6$ ($[M]^+$) 150.065376, found 150.065394 (deviation 0.1 ppm).

**Procedures for the preparation of purine (13)**: m.p. 214–216 °C [lit. [26] m.p. 214–217 °C]; $R_f$ = 0.3 (MeOH/DCM 1:9); $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta$ = 12.8–11.3 (bs, 1H), 9.09 (s, 1H), 8.88 ppm (s, 1H); $^{13}$C NMR (75 MHz, [D$_6$]DMSO): $\delta$ = 154.5, 151.8 (CH), 145.9 (CH), 145.3 (CH), 130.2 ppm; HR (LSIMS): calcd for $C_5H_4N_4$ ($[M+H]$)$^+$ 120.043722, found 120.043596 (deviation −1.0 ppm).

*Method a:* Sodium hydroxide (0.24 g, 6 mmol) was added to water (20 mL), and the mixture was stirred to solution for 5 min at room temperature. Then the hydrazino derivative **12** (0.149 g, 1 mmol) was added and the resulting mixture was stirred at reflux temperature for 12 h. After cooling to room temperature, the crude reaction mixture was neutralized with HCl 1 N (~6 mL) and extracted with ethyl acetate (3× 20 mL). Then the organic layer were collected and dried over sodium sulfate anhydrous and next distilled under vacuum to provide pure compound **13** as a white solid (95%).

*Method b:* A dispersion of NaH (60% in mineral oil, 0.24 mg, 6 mmol) was added portionwise to methanol (20 mL), and the mixture was stirred for 10 min at room temperature. Then the hydrazino derivative **12** (0.149 g, 1 mmol) was added and the resulting mixture was stirred at reflux temperature for 8 h. The solvent was evaporated and the crude was neutralized with aqueous HCl 1 N (~11 mL) and extracted with ethyl acetate (3x20 mL). Then the organic layers were combined and the crude residue was purified by flash chromatography (dichloromethane/methanol 14:1). Compound **13** was obtained as a white solid (67%).

**Procedure for the preparation of 2-chloropurine 16 from 2,6-dichloropurine (14)**: Hydrazine monohydrate (0.116 mL, 2 mmol) was added to a solution of 2,6-dichloropurine **14** (0.189 g, 1 mmol) in water (20 mL) and the mixture was stirred at reflux temperature for 30 min. Then, sodium hydroxide (0.48 g, 12 mmol) was added to the reaction, and the mixture was stirred at room temperature for 3.5 h. An analytical HPLC was carried out showing that the reaction was completed. A unique peak was detected, using a UV detector (254 nm), corresponding to the desired compound. After cooling to room temperature, the crude reaction mixture was neutralized with aqueous HCl 1 N (~11 mL) and extracted with ethyl acetate (3×20 mL). Then the organic layers were combined and dried

over anhydrous sodium sulphate and dried in vacuo to provide pure compound **16** as a light yellow solid (97%); m.p. 233–235°C [lit. [27] m.p. 231–234°C]; $R_f = 0.4$ (MeOH/DCM 1:9); $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta = 9.04$ (s, 1H), 8.68 ppm (s, 1H); $^{13}$C NMR (75 MHz, [D$_6$]DMSO): $\delta = 157.7$ (CH), 152.6 (CH), 147.8 (CH), 146.9, 128.6 ppm; HRMS (EI): calcd for $C_5H_3ClN_4$ ([*M*]$^+$) 154.004624, found 154.004474 (deviation 1.0 ppm).

To verify the process, 6-chloro-2-hydrazinepurine **15** was isolated one time by filtration. Compound **15** was obtained as a white solid (98%); m.p. >300°C [lit. [27] m.p. >300°C]; $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta = 9.12$ (bs, 1H), 8.12 (s, 1H), 4.92 ppm (bs, 2H); HR (LSIMS): calcd for $C_5H_5ClN_6$ ([*M*]$^+$) 184.026422, found 184.026904 (deviation −2.6 ppm).

**X-ray crystallographic study of compound 3d**: Crystallographic data were collected at 297 K using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods using the program SHELXS97[28] and all non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least squares techniques of $F^2$ using the program SHELXL97.[29] Hydrogen atoms were inserted in calculated positions and refined isotropically. Molecular graphics were obtained from ORTEP-3 v1.08.[30] Relevant crystal data: colorless prisms, crystal size $0.35 \times 0.32 \times 0.12$ mm, formula $C_{10}H_{11}N_3O$, $M_r = 189.22$, system monoclinic, space group $P2(1)/c$, unit cell dimensions $a = 11.7758(10)$, $b = 11.2035(10)$, $c = 7.3807(7)$ Å, $\beta = 98.1130(10)°$, $V = 963.99(15)$ Å$^3$, $Z = 4$, $\mu(Mo_{K\alpha}) = 0.088$ mm$^{-1}$, $\rho_{calcd} = 1.304$ Mg m$^{-3}$, $F(000) = 400$, measured/unique reflections 2248/1804 ($R$(int) = 0.0228), refinement method = full-matrix lest-squares on $F^2$, final $R_1(I > 2\sigma(I)) = 0.0587$ and $wR_2 = 0.1542$. CCDC-286167 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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