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PYRIDO[3,4-*b*]PYRAZINES. A NEW APPLICATION OF 2-CHLORO-3,4-DIAMINOPYRIDINE

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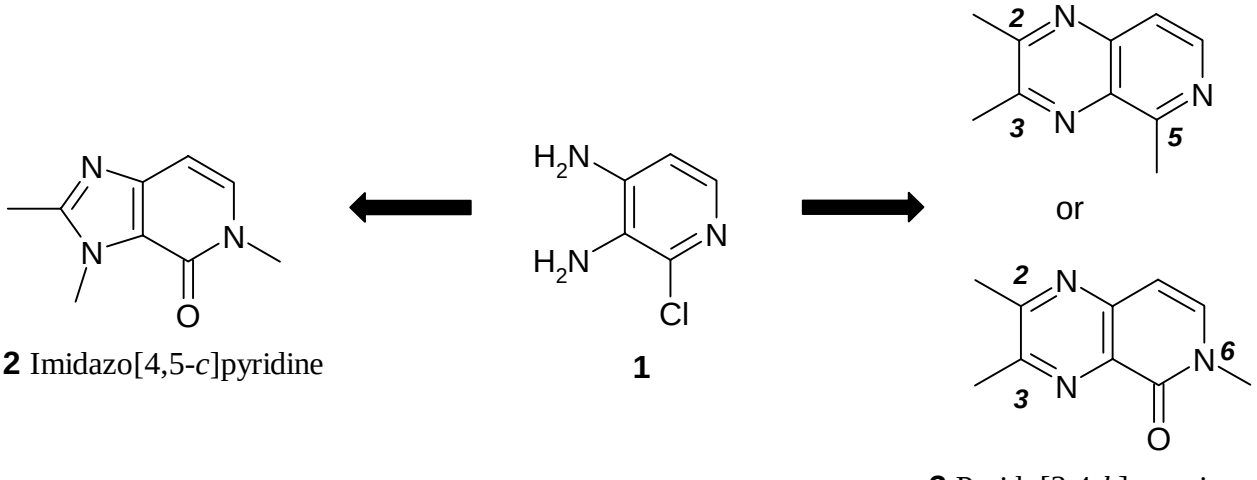
Abstract - 5-Chloropyrido[3,4-*b*]pyrazines were prepared from 1,2-dicarbonyl compounds and 2-chloro-3,4-diaminopyridine. Condensation of unsymmetrical glyoxals provided a mixture of two regiosiomers with 2-substituted pyrido[3,4-*b*]-pyrazines as the major product. The regiochemistry was unambiguously assigned by 2D-NMR experiments. C-C- and C-*N* coupling reactions of 5-chloro or 5-oxo intermediates afforded the corresponding C-5 or *N*-6 substituted derivatives.

One of the current aims in medicinal chemistry is the search for unique and patentable scaffolds. These scaffolds equipped with appropriate side chains and functional groups should give rise to new pharmacological active molecules.

In this respect 2-chloro-3,4-diaminopyridine (CDAP) (**1**) served as a starting point for the synthesis of the scaffold imidazo[4,5-*c*]pyridin-5-one (**2**) (Figure 1). Some of these 2,3,5-trisubstituted derivatives led to potent angiotensin AT_1-antagonists[1] and others to mixed AT_1-/AT_2-antagonists[2] as well. In order to find new bicyclic heterocycles from CDAP pyrido[3,4-*b*]pyrazines of the common structure (**3)** were envisaged (Figure 1).



2 Imidazo[4,5-*c*]pyridine **1** **3** Pyrido[3,4-*b*]pyrazine

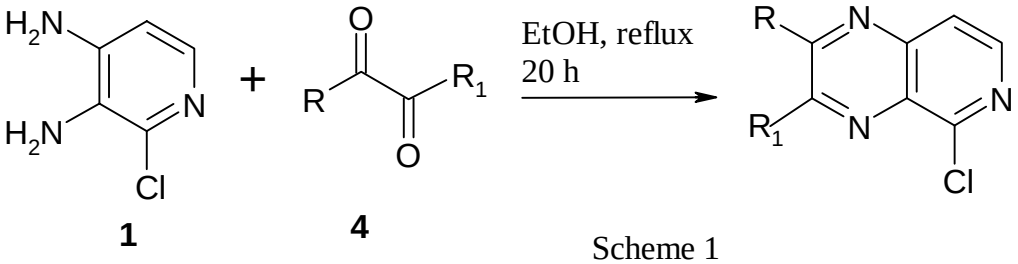
Figure. 1

A literature survey revealed only one compound 2-chloropyrido[3,4-*b*]pyrazine (**5a**) mentioned as an intermediate in a patent application[3] and the use of CDAP to form a tetracyclic compound.[4] In general

2,3-disubstituted pyrido[2,3-*b*]pyrazines and pyrido[3,4-*b*]pyrazines have been synthesized by condensing the appropriate *ortho* substituted diaminopyridine with 1,2-dicarbonyl derivatives such as **4**.[5,6] Condensation of cyclic diketo derivatives with diaminopyridines, however, led to isomeric mixtures of tetrameric heterocycles.[7,8]

In this paper the synthesis of 5-chloropyrido[3,4-*b*]pyrazines and subsequent functionalization reactions to C-5 or *N*-6 substituted derivatives together with the structural characterization of regioisomers by NMR spectroscopy is described.

In order to evaluate the reactivity of CDAP to form the 5-chloropyrido[3,4-*b*]pyrazines the commercial available 1,2-dicarbonyls such as glyoxal, diacetyl, benzil, methyl- and phenyl glyoxal were chosen. Pyrido[3,4-*b*]pyrazines (**5a** – **5f**) were prepared in moderate to good yields by condensing the respective diketo compound with CDAP in refluxing ethanol (Scheme 1). In these cases diacetyl was the least



1 **4**

5a R = R_1 = H
5b R = R_1 = Me
5c R = R_1 = Ph
5d R = Me, R_1 = H
5e R = H, R_1 = Me
5f R = Ph, R_1 = H

Scheme 1

reactive compound which led to **5b** in only 60% yield. However, methyl glyoxal converted CDAP to the corresponding regioisomers (**5d**) and (**5e**). The major isomer (**5d**) is thought to arise from attack by the more nucleophilic 3-amino group on the more electrophilic formyl function. The 2- and 3-methyl derivatives (**5d**) and (**5e**) were separated by chromatography and characterized by NMR spectroscopy.

The ^{1}H NMR spectral data, chemical shifts and coupling constants of both molecules (**5d**) and (**5e**) are depicted in Table 1.

Table 1:

Compound (**5d**)	Chemical shift (ppm)	Coupling	Coupling constant (Hz)
H1	8.59	^3J(1,2)	5.7
H2	7.95	^3J(1,2)	5.7
H3	9.07	-	-
H4	2.80	-	-
Compound (**5e**)			
H1	8.57	^3J(1,2)	5.7
H2	8.01	^3J(1,2)	5.7
H3	9.16	-	-
H4	2.81	-	-

The ^{1}H NMR spectra, the intensities of the signals, their chemical shifts and coupling constants, were very similar and it was therefore impossible to determine to which C-atom of the pyrazine ring the methyl substituent was attached.

In general for molecules of this type it proved advantageous to record HMBC spectra (**H**etero-**M**ulti-**B**ond-**C**orrelation). With standard ^{1}H-^{13}C-HMBC it was impossible to verify one of the two structures.

The problem could, however, be solved in an elegant and unambiguous fashion by observing ^{1}H-^{15}N-HMBC spectra. The results of these investigations are shown in Figure 2.

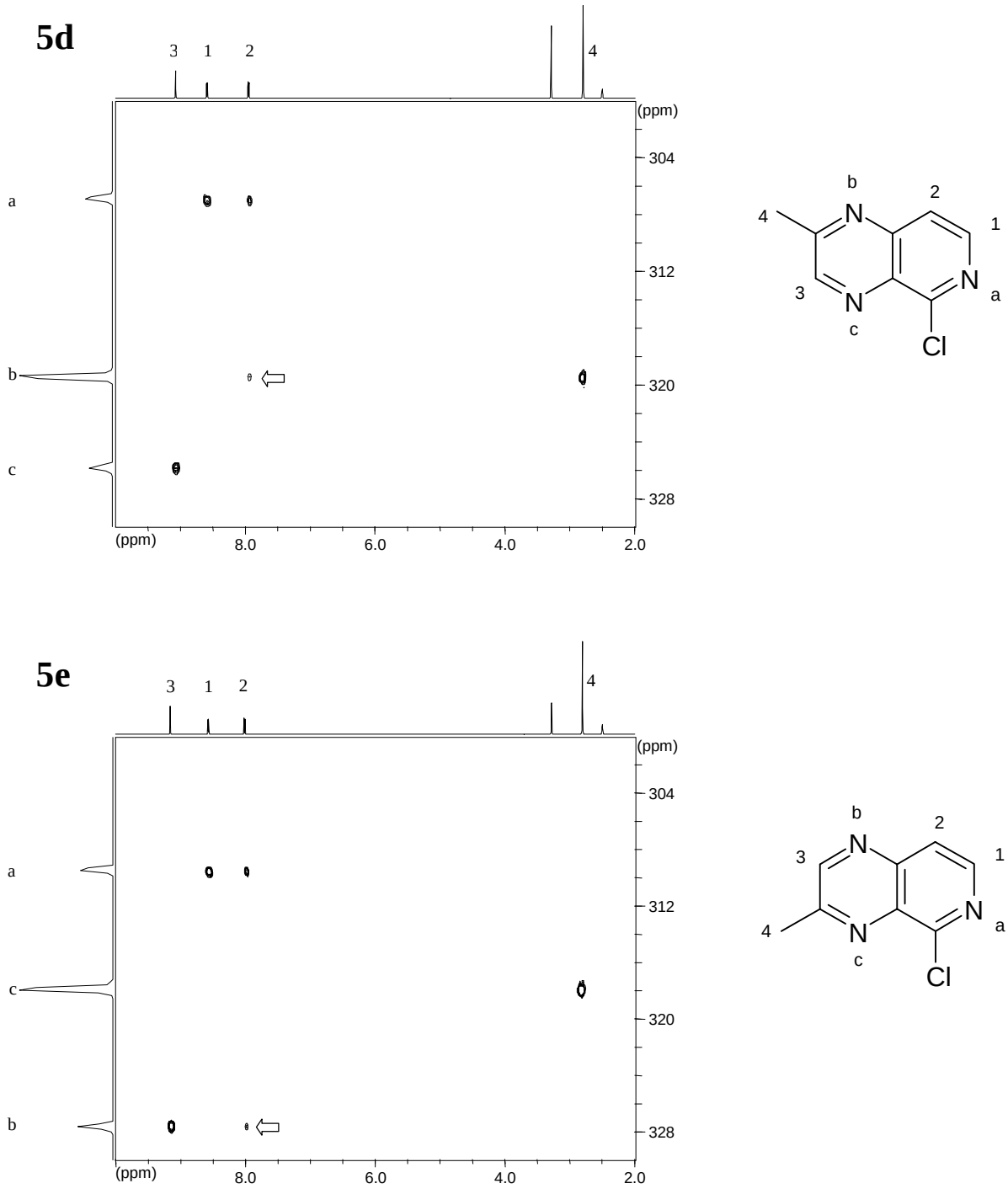


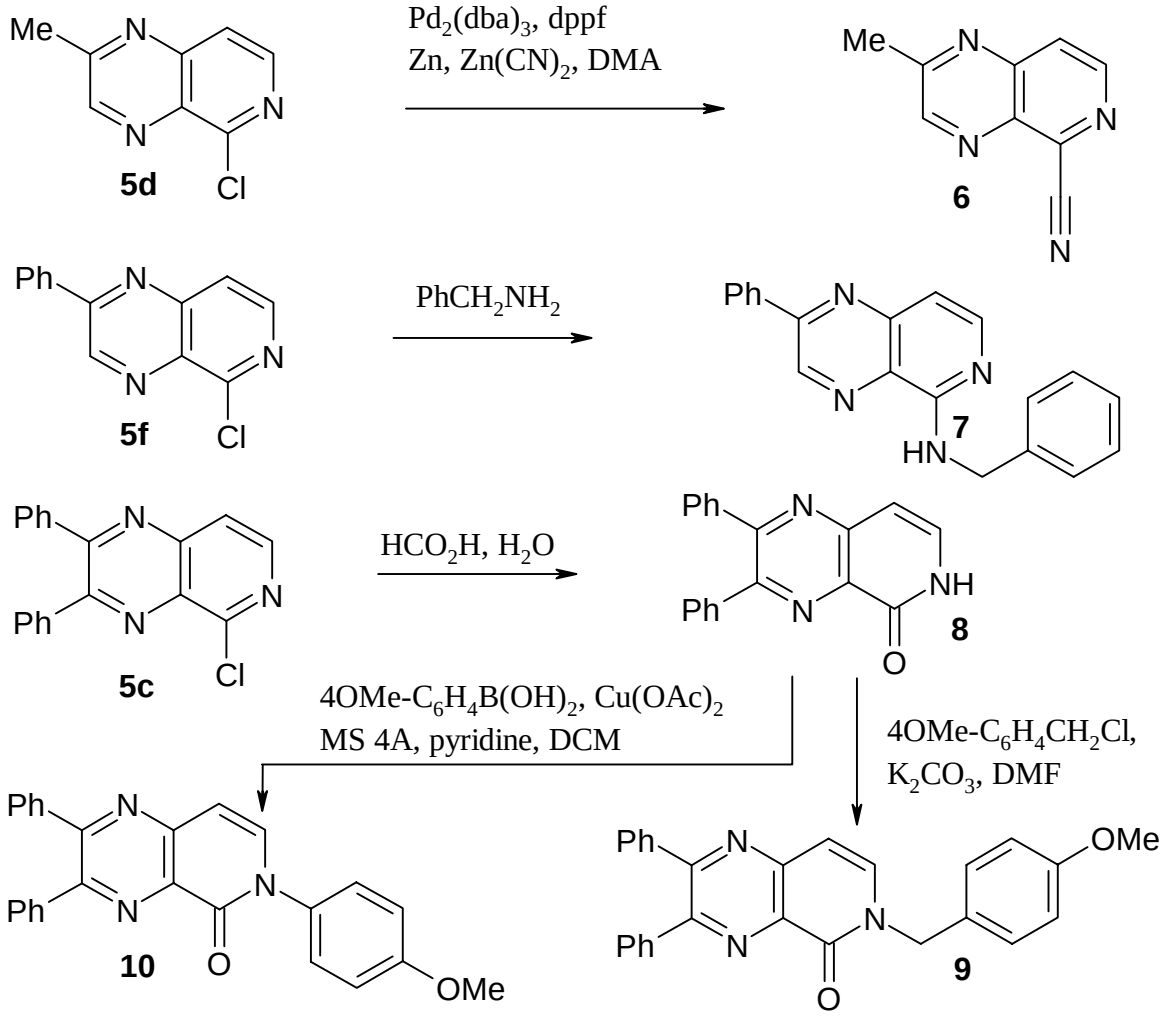
Figure. 2

The assignment of the protons and nitrogens and for that reason the position of the methyl group was now straightforward from the interpretation of the cross signals. In both molecules *proton 1* has just one coupling partner within *nitrogen a*. *Proton 2* couples with *nitrogen a* and *nitrogen b* (indicated by an arrow). So it is easily shown that *nitrogen b* and *nitrogen c* switch their places in the spectra. The cross peak from the methyl group (*4*) into *nitrogen b* and the signal *proton 3*/*nitrogen c* in the upper spectrum

confirm unambiguously the assignment to structure (**5d**), while the corresponding signals of the lower spectrum fit into structure (**5e**).

Treatment of CDAP with phenyl glyoxal gave rise to 2-phenyl derivative (**5f**) after recrystallization of the crude isomeric mixture[9] from ethanol in 79% yield. The structure of **5f** was assigned on the basis of the spectroscopic results of the methyl analogue, the mechanism, the reaction outcome (**5f** as the main product) and similar literature results with 3,4-diaminopyridine as the corresponding nucleophile.[10]

With the key intermediates (**5a** – **5f**) in hand, we focused our attention on the chloro atom in 5-position of the pyrido[3,4-*b*]pyrazine scaffold. At the outset of these studies C- and *N*-arylations at the chloro position were envisaged (Scheme 2).



Scheme 2

To extand the scope of a recently published Pd-catalyzed cyanation reaction[11] 2-methyl isomer (**5d**) was converted with $Zn(CN)_2$ as the cyanide source in the presence of catalytic amounts of Zn powder, $Pd_2(dba)_3$ and dppf to 5-cyano derivative (**6**) in 59% yield. An amination reaction without using any catalysts was investigated with the primary benzylamine. The coupling of benzylamine with compound (**5f**) gave the required adduct (**7**) in excellent yields. In order to get access to the *N*-6 nitrogen atom in the pyrido[3,4-*b*]pyrazine moiety chloro derivative (**5c**) was hydrolized in aqueous formic acid to provide 5-oxo derivative (**8**) in 91% yield. Parts of the structure of compound (**8**) can be regarded as a 2-

pyridone. In general those compounds can react as ambident nucleophiles to give mixtures of *N*/O-products. However, when compound (**8**) was alkylated with 4-methoxybenzyl chloride and potassium carbonate in dimethylformamide exclusive formation of **9** occurred in high yield. Next, a recent developed method to *N*-arylate pyridone systems was applied.[12] 4-Methoxyphenylboronic acid underwent coupling with cupric acetate and compound (**8**) to the 4-methoxy derivative (**10**). In both reactions no traces of *O*-alkylation or *O*-arylation products were found, respectively.

In summary, it has been shown that condensation of CDAP with different 1,2-dicarbonyls provided the corresponding 5-chloropyrido[3,4-*b*]pyrazines in good yields. With unsymmetrical glyoxals the 2-substituted adducts were obtained as major products. In one case this was confirmed by NMR experiments. Subsequent C-C- and C-*N* coupling reactions afforded the appropriate C-5 or *N*-6 substituted derivatives in good yields.

Therefore, the 5-chloropyrido[3,4-*b*]pyrazine scaffold can be of use as an intermediate in the design of new drug candidates.

EXPERIMENTAL

Melting points were determined with a HWS Labortechnik SGV 500 Plus melting point apparatus and are uncorrected. IR, NMR and MS spectra are in agreement with the structures cited and were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker Avance 250, AMX 300, Avance 400 or Avance DRX 500 (TMS as internal standard), and a Micromass (Manchester, England) VG 70-70E (electron-impact: EI) or 70-250SE (fast atom bombardement: FAB) at 70eV, respectively. HRMS spectra were recorded on a Autospec M from Micromass. Microanalyses were obtained with a Perkin-Elmer 240B CHN analyzer. TLC was carried out on precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from Merck KGaA (Darmstadt, Germany). Visualization was performed with UV and I_2. Yields were not optimized. The preparative chromatography was performed on Merck KGaA silica gel 60 (230-400 mesh) and all solvents were of Merck extra-pure grade. The ^{15}N-HMBC spectra were measured on a Bruker Avance 400 MHz spectrometer with about 50 mg of compound (**5d**) and (**5e**), each dissolved in 0.7 mL of DMSO-d_6 (99.95% D, Merck KGaA, Darmstadt). The spectra were obtained with a standard HMBC pulse programme (inv4gplplrnd) with z-gradients (relevant parameters: SW(^{1}H)= 4006 Hz, SW(^{15}N)= 4056 Hz, AQ= 0.13s, TD= 1024pts., RD= 1.5s, NS= 96, number of FID´s= 256, J(H,N)= 8 Hz). Data were multiplied with a pure sinebell window in both directions and zero-filled to give a 2K ∗ 512 Matrix after Fourier-transformation. The internal standard in ^{1}H direction was TMS, in ^{15}N direction was made a standard calibration with NH_3(l) as reference set to zero.

5-Chloropyrido[3,4-*b*]pyrazine (5a): To 30 mL of ethanol was added 2.12 mL (13.93 mmol) of glyoxal (30% in water) and 2.0 g (13.93 mmol) of 2-chloro-3,4-diaminopyridine (**1a**). The mixture was refluxed for 20 h. On cooling the crude precipitated product was filtered off, washed with 20 mL of ethanol and dried. The resulting product was purified by recrystallization from ethanol to yield 1.88 g (81.5 %) of **5a**: mp 141-143°C. MS (EI): m/z = 165 (M^+, 100%), 167 (35%). ^{1}H NMR (DMSO-d_6) δ

9.26 (d, *J* = 1.8 Hz, 1H), 9.19 (d, *J* = 1.8 Hz, 1H), 8.65 (d, *J* = 5.7 Hz, 1H), 8.07 (d, *J* = 5.7 Hz, 1H). HRMS calcd for (M^+) m/z 165.0094, found m/z 165.0095. *Anal.* Calcd for $C_7H_4N_3Cl$: C, 50.78; H, 2.43; N, 25.38. Found: C, 50.40; H, 2.50; N, 25.70.

5-Chloro-2,3-dimethylpyrido[3,4-*b*]pyrazine (5b): This compound was prepared from CDAP and diacetyl (**4** R, R' = Me) by the method described above with a yield of 60% after recrystallization from ethanol: mp 121-123°C. MS (EI): m/z = 193 (M^+, 100%), 195 (35%). ^{1}H NMR (DMSO-d_6) δ 8.50 (d, *J* = 5.6 Hz, 1H), 7.90 (d, *J* = 5.6 Hz, 1H), 2.76 (s, 6H). HRMS calcd for (M^+) m/z 193.0407, found m/z 193.0407. *Anal.* Calcd for $C_9H_8N_3Cl$: C, 55.83; H, 4.16; N, 21.70. Found: C, 55.70; H, 4.10; N, 22.00.

5-Chloro-2,3-diphenylpyrido[3,4-*b*]pyrazine (5c): This compound was prepared from CDAP and benzil (**4** R, R' = Ph) by the method described above with a yield of 91% after recrystallization from ethanol: mp 146-148°C. MS (EI): m/z = 317 (M^+,100 %), 319 (33%). ^{1}H NMR (DMSO-d_6) δ 8.64 (d, *J* = 5.7 Hz, 1H), 8.08 (d, *J* = 5.7 Hz, 1H), 7.60-7.34 (m, 10H). HRMS calcd for (M^+) m/z 317.0720, found m/z 317.0728. *Anal.* Calcd for $C_{19}H_{12}N_3Cl$: C, 71.81; H, 3.81; N, 13.22. Found: C, 71.95; H, 3.60; N, 13.44.

5-Chloro-2-methylpyrido[3,4-*b*]pyrazine (5d) and 5-Chloro-3-methylpyrido[3,4-*b*]pyrazine (5e): These compounds were prepared from CDAP and methyl glyoxal (**4** R = H, R' = Me) by the method described above and provided after chromatography on silica gel with dichloromethane/ *tert*-butyl methyl ether = 95/5 82% of **5d** and 12% of **5e**. **5d**: mp >280°C (from ethanol). MS (EI): m/z = 179 (M^+, 100%), 181 (33%). HRMS calcd for (M^+) m/z 179.0250, found m/z 179.0248. *Anal.* Calcd for $C_8H_6N_3Cl$: C, 53.50; H, 3.37; N, 23.40. Found: C, 53.50; H, 3.40; N, 23.00. **5e**: mp 145-147°C. MS (ei): m/z = 179 (M^+, 100%), 181 (35%). HRMS calcd for (M^+) m/z 179.0250, found m/z 179.0250. *Anal.* Calcd for $C_8H_6N_3Cl$: C, 53.50; H, 3.37; N, 23.40. Found: C, 53.40; H, 3.50; N, 23.30.

5-Chloro-2-phenylpyrido[3,4-*b*]pyrazine (5f): This compound was prepared from CDAP and phenyl glyoxal monohydrate (**4** R = H, R' = Ph) by the method described above with a yield of 79% after recrystallization of the crude isomeric mixture from ethanol: mp 189-190°C. MS (EI): m/z = 241 (M^+, 100%), 243 (35%). ^{1}H NMR (DMSO-d_6) δ 9.80 (s, 1H), 8.64 (d, *J* = 5.7 Hz, 1H), 8.46-8.36 (m, 2H), 8.07 (d, *J* = 5.7 Hz, 1H), 7.71-7.62 (m, 3H). HRMS calcd for (M^+) m/z 241.0402, found m/z 241.0404. *Anal.* Calcd for $C_{13}H_8N_3Cl$: C, 64.61; H, 3.34; N, 17.39. Found: C, 64.20; H, 3.50; N, 17.10.

2-Methylpyrido[3,4-*b*]pyrazine-5-carbonitrile (6): To 250 mg (1.376 mmol) of 5-chloro-2-methylpyrido[3,4-*b*]pyrazine (**5d**), 25 mg (2 mol %) of tris(dibenzylidenacetone)palladium(0), 30.0 mg (4 mol %) of 1,1'-bis(diphenylphosphino)ferrocene, 10.5 mg (12 mol %) of zinc dust and 97.0 mg (0.827 mmol) of zinc cyanide was added 10.0 mL of *N*,*N*-dimethylacetamide under a nitrogen atmosphere. The mixture was heated at 120°C for 24 h. It was cooled to rt, diluted with ethyl acetate, and then washed with 2N ammonium hydroxide solution and brine. After drying over sodium sulfate,

the ethyl acetate solution was evaporated under reduced pressure. The residue was chromatographed on silca gel using ethyl acetate / hexane (60:40) to provide 160 mg (59%) of **6**: mp >170°C (decomp, from ethanol). IR (KBr) 2235 cm^{-1}. MS (FAB): m/z = 171 ($M+H^+$, 100%). ^1H NMR (DMSO-d_6) δ 9.16 (s, 1H), 8.96 (d, *J* = 5.7 Hz, 1H), 8.28 (d, *J* = 5.7 Hz, 1H), 2.83 (s, 3H). HRMS calcd for (M^+) m/z 170.0592, found m/z 170.0595. *Anal.* Calcd for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.92. Found: C, 63.46; H, 3.49; N, 32.71.

Benzyl-(2-phenylpyrido[3,4-*b*]pyrazin-5-yl)amine (**7**)**:** To 20 mL of benzylamine was added 1.06 g (4.355 mmol) of 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine (**5f**). The mixture was stirred at 130°C for 4 h. After cooling, it was partitioned between brine and ethyl acetate. The organic extract was washed with 10% hydrochloric acid. The precipitated solid was collected and dried. The resulting product was purified by recrystallization from ethanol to yield 1.345 g (99%) of **7**: mp 250-252°C. MS (FAB): m/z = 313 ($M+H^+$,100 %). ^1H NMR (DMSO-d_6) δ 10.32 (br s, 1H), 9.61 (s, 1H), 8.40 (dd, *J* = 2.3 und *J* = 3.7 Hz, 2H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.70-7.62 (m, 3H), 7.51 (dd, *J* = 7.3 und *J* = 1.4 Hz, 2H), 7.41-7.28 (m, 3H), 7.25 (d, *J* = 7.0 Hz, 1H), 4.99 (d, *J* = 6.6 Hz, 2H). HRMS calcd for (M^+) m/z 312.1375, found m/z 312.1374. *Anal.* Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.95; H, 5.03; N, 17.64.

2,3-Diphenyl-6*H*-pyrido[3,4-*b*]pyrazin-5-one (8): To 15 mL of formic acid and 5 ml of water was added 1.0 g (3.147 mmol) of 5-chloro-2,3-diphenylpyrido[3,4-*b*]pyrazine (**5c**). The mixture was stirred at 80°C for 12 h. On cooling the crude precipitated product was filtered off, washed with 20 mL water and dried. The resulting product was purified by recrystallization from ethanol to yield 857 mg (91%) of **8**: mp > 300°C. IR (KBr) 1665 cm^{-1}. MS (EI): m/z = 299 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.57 (d, *J* = 7.3 Hz, 1H), 7.52-7.29 (m, 10H), 6.71 (d, *J* = 7.3 Hz, 1H). HRMS calcd for (M^+) m/z 299.1059, found m/z 299.1058. *Anal.* Calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 75.91; H, 4.50; N, 14.09.

6-(4-Methoxybenzyl)-2,3-diphenyl-6*H*-pyrido[3,4-*b*]pyrazin-5-one (9): To 50 mL of dimethylform-amide was added 370 mg (1.236 mmol) of 2,3-diphenyl-6*H*-pyrido[3,4-*b*]pyrazin-5-one (**8**). This mixture was treated with 205 mg (1.483 mmol) of potassium carbonate and 0.2 mL (1.483 mmol) of 4-methoxybenzyl chloride. The reaction mixture was allowed to stir at rt over night. On diluting with water the crude precipitated product was filtered off, washed with 50 mL water and dried. The resulting product was purified by recrystallization from ethanol to yield 492 mg (91%) of **9**: mp 285-287°C. IR (KBr) 1660 cm^{-1}. MS (FAB): m/z = 420 ($M+H^+$, 35%). ^1H NMR (DMSO-d_6) δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.52-7.30 (m, 12H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.21 (s, 2H), 3.73 (s, 3H). HRMS calcd for (M^+) m/z 419.1633, found m/z 419.1625. *Anal.* Calcd for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C,77.61 ; H, 5.14; N, 10.30.

6-(4-Methoxyphenyl)-2,3-diphenyl-6*H*-pyrido[3,4-*b*]pyrazin-5-one (10): A mixture of 750 mg (2.5 mmol) of 2,3-diphenyl-6*H*-pyrido[3,4-*b*]pyrazin-5-one (**8**) , 1.14 g (7.5 mmol) of 4-methoxyphenyl-boronic acid, 253 mg (5.5 mmol) of anhydrous cupric acetate, 1.5 g of activated 4 Å molecular sieve and 1.0 mL (12.4 mmol) of pyridine, in dichloromethane (40 mL) was treated at rt for 48 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with saturated sodium bicarbonate solution and 10% hydrochloric acid in succession, and then dried and evaporated. The resulting product was purified by recrystallization from ethanol to yield 793 mg (78%) of **10**: mp 155-156°C. IR (KBr) 1679 cm^{-1}. MS (EI): m/z = 405 (M^+, 100%). ^1H NMR (DMSO-d_6) δ 7.81 (d, *J* = 7.6, 1H), 7.52-7.34 (m, 12H), 7.11 (d, *J* = 8.9, 2H), 6.84 (d, *J* = 7.6, 1H), 3.84 (s, 3H). HRMS calcd for (M^+) m/z 405.1477, found m/z 405.1474. *Anal.* Calcd for $C_{26}H_{19}N_3O_2$: C, 77.02; H, 4.72; N, 10.36. Found: C, 76.80; H, 4.60; N, 9.90.

REFERENCES

1. W. W. K. R. Mederski, D. Dorsch, H.-H. Bokel, N. Beier, I. Lues, and K.-O. Minck, *J. Med. Chem.*, 1994, **37**, 1632.
2. W. W. K. R. Mederski, D. Dorsch, M. Oßwald, H. Schwartz, N. Beier, M. Christadler, K.-O. Minck, and P. Schelling, *Eur. J. Med. Chem.*, 1997, **32**, 479.
3. G. McCort, C. Hoornaert, C. Cadhilac, O. Duclos, and E. Guilpain, *PCT Int. Appl*., WO 94 42712 *(Chem. Abstr., 1998, **129**, 275934)*.
4. Z. Talik and E. Plazek, *Rosz. Chem.*, 1956, **30**, 1139.
5. M. Israel and A. R. Day, *J. Org. Chem.*, 1959, **24**, 1455.
6. F. F. Duarte and F. D. Popp, *J. Heterocycl. Chem.*, 1994**,** **31**, 819.
7. N. Vinot and P. Maitte, *J. Heterocycl. Chem.*, 1989**,** **26**, 1013.
8. C. D. Gabbutt, J. D. Hepworth, and B. M. Heron, *Tetrahedron*, 1994, **50**, 7865.
9. HPLC analysis of the crude product indicates a ratio of 89% of **5f** to 7% of 5-chloro-3-phenylpyrido-[3,4-*b*]pyrazine.
10. S. Kano and Y. Yuasa, *J. Heterocycl. Chem.*, 1983**,** **20**, 769.
11. F. Jin and P. N. Confalone, *Tetrahedron Lett.*, 2000, **41**, 3271.
12. W. W. K. R. Mederski, M. Lefort, M. Germann, and D. Kux, *Tetrahedron*, 1999, **55**, 12757.