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SYNTHESIS OF MONO- AND DISUBSTITUTED 1H-IMIDAZO [1,2-b] PYRAZOLES

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The improved synthesis of 1H-imidazo[1,2-b]pyrazole **1** and of mono- and disubstituted derivatives is described and representative experimental procedures are given. Namely, 2-, 3-, 7- and 6-monosubstituted (**2-15k**), 2,3- and 6,7-disubstituted (**16,17**) compounds are prepared and characterized.

The 1H-imidazo[1,2-b]pyrazole nucleus[4,5] (Figure 1) and some of its derivatives[6-11] have been previously synthesized and used as starting materials for color photographic couplers and dyes,[12,13] or tested in biological assays.[14-16]

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Having already studied derivatives of this nucleus as CNS agents,[17] we prepared other derivatives to be characterized biologically. We prepared and tested the unsubstituted ring, some 2-, 3-, 6- and 7-monosubstituted compounds and some 6,7- and 2,3-disubstituted products (see Figure 1 for the numbering).

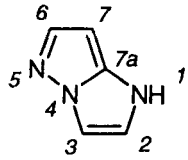
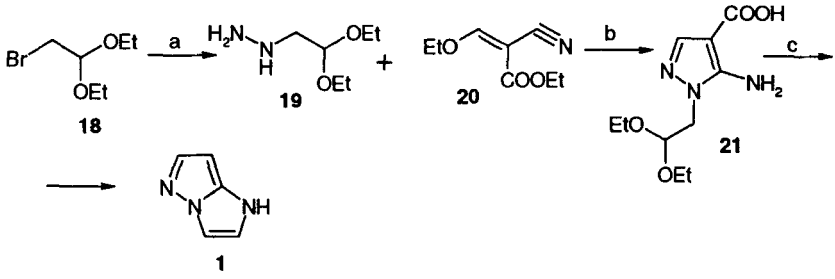


Figure 1

Chemistry

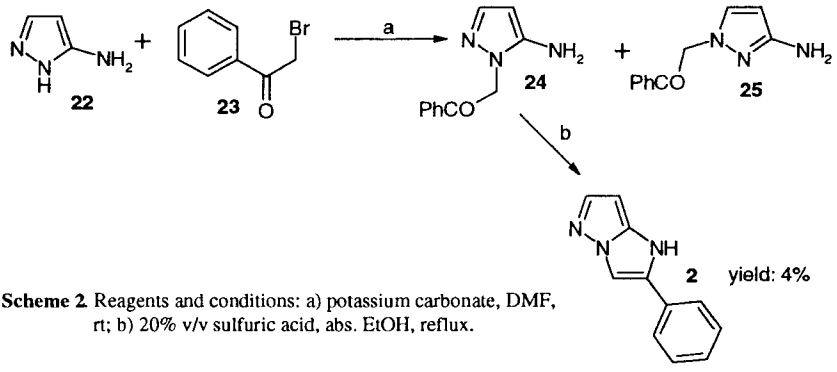
1H-Imidazo[1,2-b]pyrazole 1.- This compound was prepared improving the already reported synthesis reported by our research group.[17] The synthetic route is depicted in Scheme 1.



Scheme 1. Reagents and conditions: a) hydrazine hydrate, abs. EtOH, reflux; b) toluene, reflux, then 4N NaOH, reflux, then 20% HCl; c) 20% v/v sulfuric acid, abs. EtOH, reflux.

The synthesis of the key intermediate **19** was improved (better yields, no distillation of the hydrazine, see the Experimental Protocols).

2-monosubstituted derivatives.- The reaction of 3-aminopyrazole **22** with α-bromoacetophenone **23** (Scheme 2) produced an equimolar mixture (^{1}H NMR of the crude) of the desired 1-alkyl-5-aminopyrazole **24** and the isomeric 1-alkyl-3-aminopyrazole **25**. A chromatography was required and the total yield of **2** was unsatisfactory. No other 2-substituted derivatives were prepared.

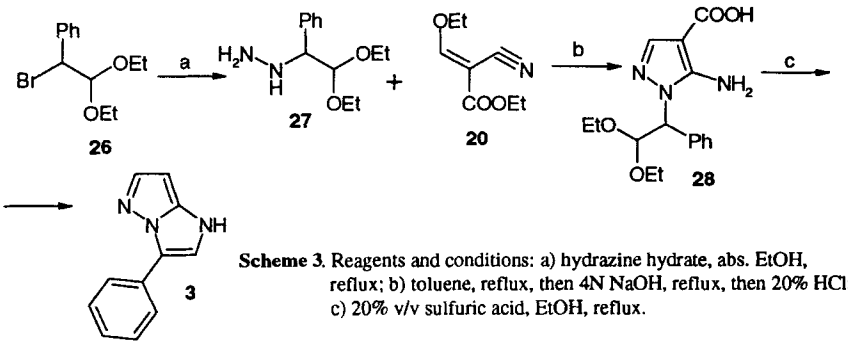


Scheme 2. Reagents and conditions: a) potassium carbonate, DMF, rt; b) 20% v/v sulfuric acid, abs. EtOH, reflux.

3-monosubstituted derivatives.- The phenyl hydrazine **27** ,prepared from bromide **26**[18], was used to produce eventually the 3-phenyl derivative **3** as seen for the synthesis of **1** (Scheme 3).

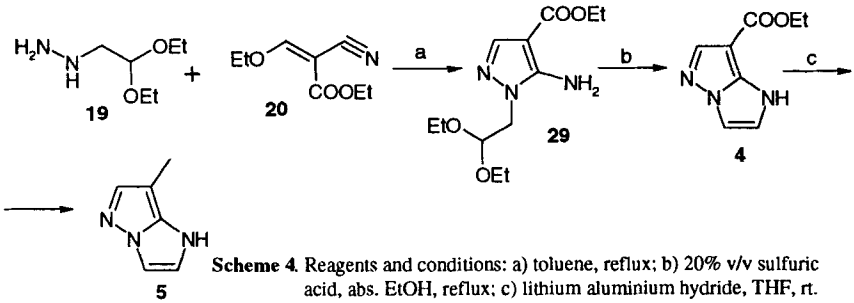
The yield for the cyclization to pyrazole with hydrazine **27** was worse than with **19**, and no other hydrazines were prepared to give other 3-substituted nuclei.

7-monosubstituted derivatives.- The compounds **4-11c** were prepared. Compounds **4** and **5** were prepared from condensation of compounds **19** and **20**,



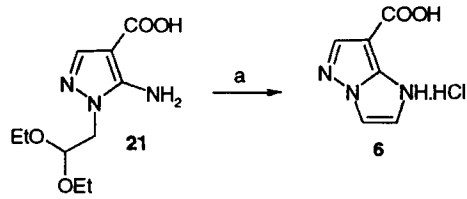
Scheme 3. Reagents and conditions: a) hydrazine hydrate, abs. EtOH, reflux; b) toluene, reflux, then 4N NaOH, reflux, then 20% HCl; c) 20% v/v sulfuric acid, EtOH, reflux.

isolating the intermediate aminoester **29** which was then cyclized to give **4**. Reduction of compound **4** produced compound **5** (Scheme 4).



Scheme 4. Reagents and conditions: a) toluene, reflux; b) 20% v/v sulfuric acid, abs. EtOH, reflux; c) lithium aluminium hydride, THF, rt.

The acid **6** was prepared from **21** which was cyclized to give **6** using ethereal HCl (Scheme 5). Its stability as a solid hydrochloric acid salt was good.

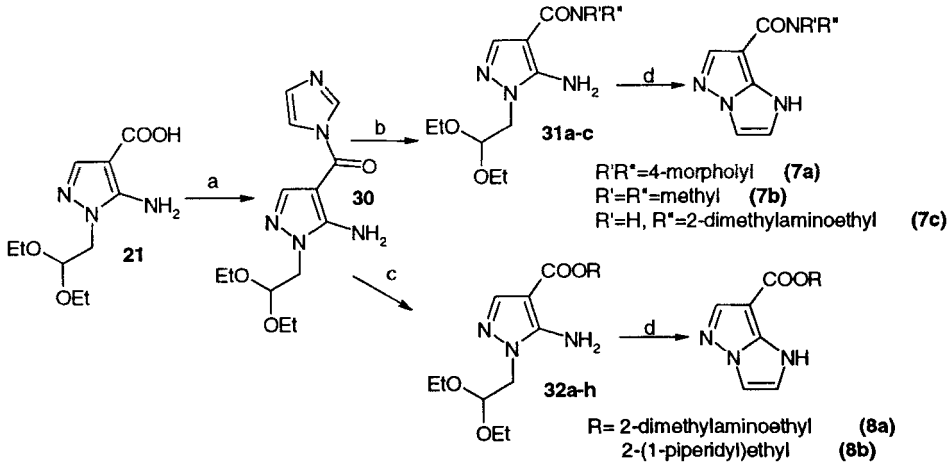


Scheme 5. Reagents and conditions: a) ethereal HCl, rt.

These cyclative acidic conditions in an apolar solvent were used whenever the 1H-imidazo[1,2-b]pyrazole was sensitive to strong acidic aqueous conditions.

Synthesis of 7-carboxyamides or esters was attempted from the ester **4**, but amidation of **4** with amines did not work and hydrolysis of the ester function resulted in the free acid which underwent decarboxylation to give **1**.

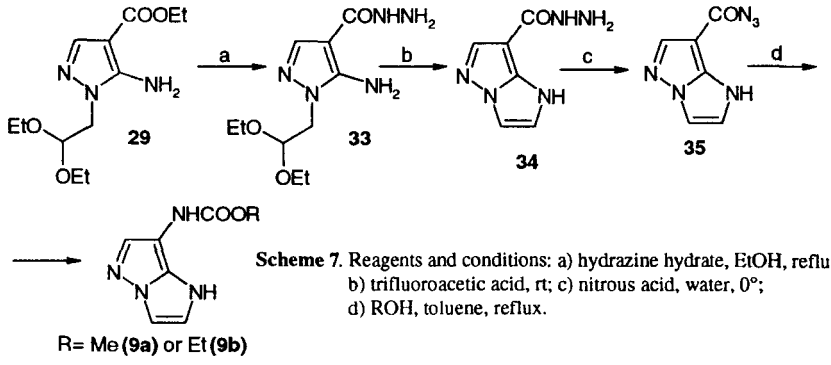
Compound **21** was used for the synthesis of the amides **7a-c** and the esters **8a-h** via its carbonylimidazolide **30**. This compound reacted with amines to give the amidopyrazoles **31a-c** and with alcohols to give esters **32a-h**. These compounds were cyclized to compounds **7a-8h** (Scheme 6).



Scheme 6. Reagents and conditions: a) CDI, THF, rt; b) R'R"NH, THF, rt; c) ROH, NaH, THF, rt; d) 20% v/v sulfuric acid, EtOH, reflux, or ethereal HCl, rt.

The stable imidazolide **30** was purified by chromatography. It reacted easily with amines, moderately with alcohols (NaH as base was required).

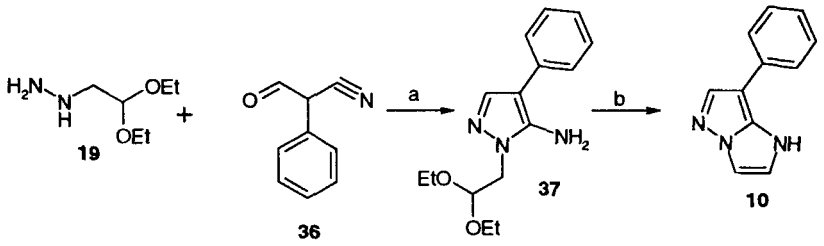
Compounds **9a,b** were prepared from **29** which reacted with $N_2H_4.H_2O$ to give **33**. This was cyclized to the hydrazone **34**, which was rearranged via acylazide **35** to produce the carbamates **9a,b** (Scheme 7).



Scheme 7. Reagents and conditions: a) hydrazine hydrate, EtOH, reflux; b) trifluoroacetic acid, rt; c) nitrous acid, water, 0°; d) ROH, toluene, reflux.

Surprisingly **29** reacted smoothly with hydrazine, while it did not react with amines and esters.

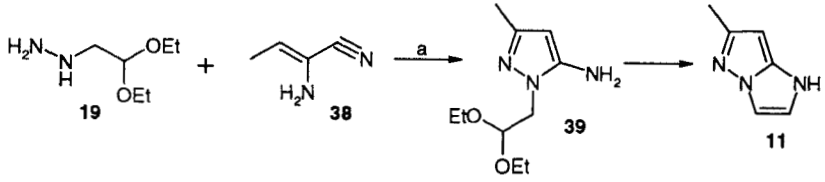
The phenyl derivative **10**[16] was prepared via condensation of **19** with aldehyde **36** and cyclization of **37** to give the desired compound (Scheme 8).



Scheme 8. Reagents and conditions: a) toluene, reflux; b) 20% v/v sulfuric acid, EtOH, reflux.

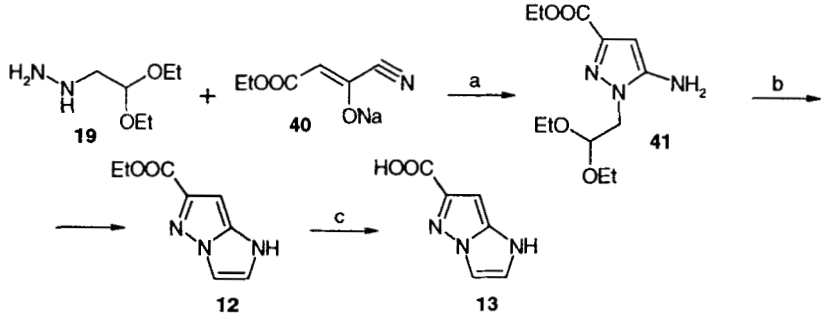
6-monosubstituted derivatives.- Compounds **11-15k** were prepared.

Compound **11**[19] was prepared via condensation of **19** with 2-aminocrotonitrile **38** to give the pyrazole **39** which was then cyclized in acidic conditions (Scheme 9).



Scheme 9. Reagents and conditions: a) hydrazine hydrate, abs. EtOH, reflux; b) EtOH, reflux; c) 20% v/v sulfuric acid, EtOH, reflux.

Compounds **12** and **13** were prepared from the condensation of the nitrile **40**[20] with **19**, followed by acidic cyclization of pyrazole **41** to produce the ester **12** which was then hydrolyzed to the free acid **13** (Scheme 10).

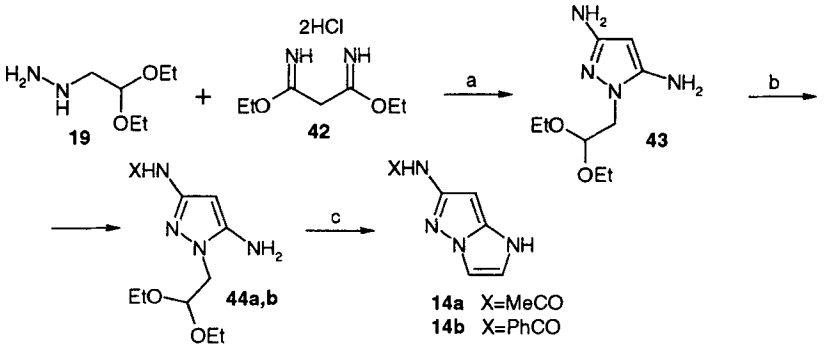


Scheme 10. Reagents and conditions: a) 20% v/v sulfuric acid, chloroform, reflux; b) ethereal HCl, rt; c) 4N NaOH, rt.

A stoichiometric amount of sulfuric acid in water/$CHCl_3$ was used, just to neutralize the sodium salt of **40** without ionization of compound **19**. The unstable

cyanoketone which derived from **40** was immediately extracted in $CHCl_3$ avoiding side reactions and probably also stabilizing the final product.

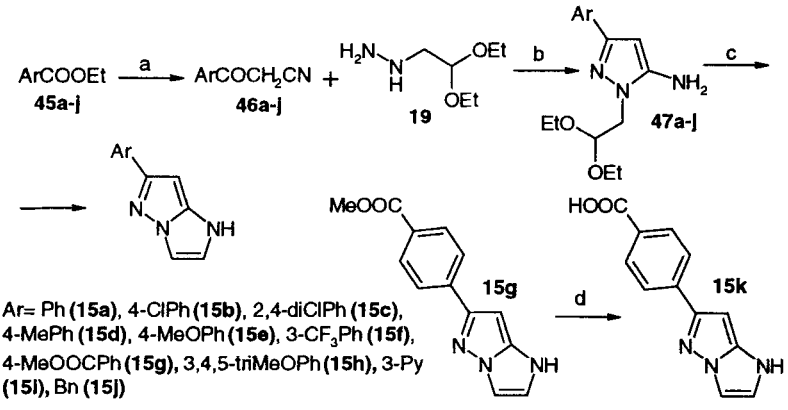
Compounds **14a,b** were prepared via the diimidate dihydrochloride **42** which was condensed with **19**, acylated with acetic or benzoic anhydride and cyclized with ethereal HCl (Scheme 11).



Scheme 11. Reagents and conditions: a) aq. potassium carbonate, EtOH, reflux; b) anhydride, TEA, methylene chloride, rt; c) ethereal HCl, rt.

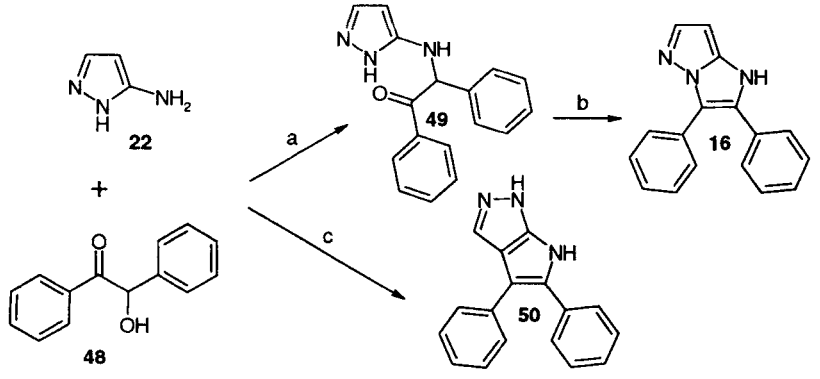
Compound **42** was neutralized "in situ" with carbonate to give the unstable base which reacted immediately with compound **19**. Cyclization of compound **43** was also tried (as in step c, Scheme 11), but the 6-amino derivative was never isolated due to decomposition during any workup procedure. Acylation of compound **43** was fully regioselective, probably due to the sterical hindrance around the 5-amino group.

Compounds **15a-k** were prepared *via* condensation of an aryl ester (**45a-j**) with MeCN.[21] Condensation of the β-ketonitriles **46a-j** with **19** and cyclization of the pyrazoles **47a-j** produced compounds **15a-j** (Scheme 12). Compound **15k** was hydrolysed to give **15j**. Some of these compounds were previously prepared.[14,16]



Scheme 12 Reagents and conditions: a) acetonitrile, NaH, toluene, reflux; b) EtOH, reflux; c) 20% v/v sulfuric acid, EtOH, reflux; d) LiOH, water/dioxane, rt.

2,3-disubstituted derivatives.- The previously unreported compound **16** was prepared using a known route[22] which is shown in Scheme 13.

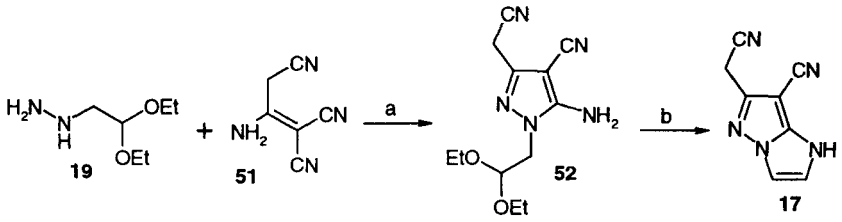


Scheme 13 Reagents and conditions: a) tetraline, 230 °C; b) quinoline, 250 °C; c) trifluoroacetic acid, rt.

While the route through the intermediate **49** was complex and the yields of **16** poor, acidic conditions as in step c, Scheme 13 produced the pyrrolopyrazole

50. The synthesis of other 2,3-disubstituted derivatives was abandoned.

6,7-disubstituted derivatives.- Synthesis of compound **17** was performed as depicted below (Scheme 14).



Scheme 14. Reagents and conditions: a) EtOH, reflux; b) 20% v/v sulfuric acid, EtOH, reflux.

Condensation of **19** with malononitrile dimer **51** produced the pyrazole **52**, then cyclized to **17**. No other 6,7-disubstituted derivatives were prepared.

Pharmacology

The unsubstituted compound **1** together with compounds **2-17** were submitted to a general pharmacological screening (data not shown). The previously tested compounds confirmed their activities, while the new ones did not show any significant biological activity worth processing further this class of derivatives.

Experimental protocols

Solvents and reagents were purified and dried by standard techniques.[23] Solvents were removed using a Buchi EL 131 rotary evaporator at bath

temperatures varying from rt to 50 °C. The reactions and the final compounds were analyzed by direct phase TLC using Merck Kieselgel 60 F_{254} thin-layer plates with eluent mixtures including CH_2Cl_2, MeOH, AcOEt and *n*-heptane. IR spectra ($CDCl_3$ solution) were recorded on a Perkin-Elmer 850 spectrometer and the values are reported in cm^{-1} (υ). ^1H NMR spectra were recorded at 200 MHz with a Bruker AC 200 at 303 °K in $CDCl_3$. The chemical shifts (δ) are reported in ppm downfield from the internal reference, tetramethylsilane (TMS, δ 0.00). A Model 1106 Carlo Erba instrument was used for elemental analysis using standard techniques.

1H-Imidazo[1,2-b]pyrazole ***1***.- To a solution of $N_2H_4.H_2O$ (303 mL, 6.25 moles) in abs. EtOH (625 mL) stirred at reflux **18** (192.5 mL, 1.25 moles) was added dropwise in 45 min. The cloudy solution was heated for additional 3 h, then the solvent was removed at reduced pressure at 40 °C. The residue was taken up with NaOH (35% w/v, 150 mL) and NaCl (25 g) and the resulting solution was extracted with toluene (2x625 mL). The organic phase (1500 mL) was titrated by GLC showing the presence of pure **19** (149.5 g, 1.01 moles, 81.0%).

This solution was immediately treated under N_2 atmosphere with **20** (178 g, 1.052 moles) and stirred at rt overnight. The reaction mixture was then heated and an azeotrope toluene/EtOH/water was distilled around 70 °C. After 3 h the solution was evaporated giving a red oil (340 g) which contained 10% toluene (^1H NMR). To this residue 4N NaOH (2122 mL) was added and the solution was

heated to 110 °C for 2 h. After cooling the aqueous phase was extracted with CH_2Cl_2 (2 x 450mL), and the organic phase was washed with brine (125 mL). The pooled aqueous phase was cooled at 5 °C, then HCl (20% w/v, 1290 mL) was added until pH 4.5. The obtained solid was filtered and washed repeatedly with water, oven dried at 45 °C at reduced pressure yielding pure **21** as a white solid, m.p. 128 °C (182.7 g, 751 mmoles, 74.5%).

A solution of **21** (182.7 g, 751 mmoles) in abs. EtOH (183 mL) and 20% v/v H_2SO_4 (1279 mL) was heated under stirring at 75 °C for 75 minutes. After cooling at rt the mixture was poured into crushed ice (2 L). Solid $NaHCO_3$ was added portionwise (T<10 °C) until pH 9 was reached (1500 g). The solid formed was filtered off and washed with water (250 mL). The aqueous phase was extracted with AcOEt (3x920 mL), then the organic phase was dried (Na_2SO_4) and evaporated. Recrystallization from water produced 1H-imidazo[1,2-b]pyrazole **1** as pale yellow crystals, m.p. 148 °C (68.9 g, 643 mmoles, 85.5%). R_f 0.44 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 55.94; H, 4.80; N, 39.11, calculated for $C_5H_5N_3$ C, 56.06; H, 4.71; N, 39.23%; $\upsilon(cm^{-1})$ 3140 (NH); $\delta_H(d_6\text{-DMSO})$, 5.60 (d,1H,2-H), 7.15 (d,1H,7-H), 7.45 (d,1H,3-H), 7.50 (d,1H,6-H), 11.45 (b,1H,NH).

2-Phenyl-1H-imidazo[1,2-b]pyrazole **2**.- Dry K_2CO_3 (1.49 g, 10.83 mmoles) and **23** (2.16 g, 10.83 mmoles) were added to a stirred solution of **22** (900 mg, 10.83 mmoles) in DMF (6 mL) at rt. After 2.5 h water (50 mL) was added and the suspension was extracted with AcOEt. The organic phase was dried (Na_2SO_4) and evaporated at 15 mm Hg. The solid residue was chromatographed

on silica gel (AcOEt/*n*-heptane 1/1) to give **24** as a white solid, m.p. 137 °C (260 mg, 1.29 mmoles, 12.0%).

A solution of **24** (260 mg, 1.29 mmoles) in abs. EtOH (2.5 mL) and 20% v/v H_2SO_4 (17 mL) was refluxed for 45 min. After cooling at rt, the pH was brought to 8 with solid $NaHCO_3$ and the solution was evaporated at 15 mm Hg. The residue was taken up with water and extracted with AcOEt, the organic phase was dried (Na_2SO_4) and concentrated to give a solid residue (225 mg). This was chromatographed on silica gel (AcOEt/*n*-heptane 1/4) to give 2-phenyl-1H-imidazo[1,2-b]pyrazole **2** as a white solid, m.p. 133 °C (59 mg, 0.322 mmoles, 25.0%). R_f 0.52 (CH_2Cl_2/MeOH 95/5); microanalysis: found C, 71.98; H, 5.06; N, 22.80, calculated for $C_{11}H_9N_3$ C, 72.11; H, 4.95; N, 22.94%; $\upsilon(cm^{-1})$ 3230 (NH); $\delta_H(CDCl_3)$ 6.20 (d,1H,7-H), 7.05 (s,1H,3-H), 7.30-7.90 (m,6H,Arom. and 6-H), 12.10 (b,1H,NH).

3-phenyl-1H-imidazo[1,2-b]pyrazole **3**.- To a solution of $N_2H_4.H_2O$ (3.0 mL, 62.5 mmoles) in abs. EtOH (6.5 mL) stirred at reflux **26**[18] (3.41 g, 12.5 mmoles) was added dropwise in 45 minutes. The cloudy solution was heated for 6 h, then the solvent was removed at reduced pressure at 40 °C. The residue was taken up with NaOH (35% w/v, 5 mL) and NaCl (1 g) and the resulting solution was extracted with toluene (3x10 mL). The organic phase (30 mL) was titrated by GLC showing the presence of pure **27** (1.05 g, 4.69 mmoles, 37.5%).

This solution was immediately treated under N_2 atmosphere with **20** (795 mg, 4.75 mmoles) and stirred at rt overnight. The reaction mixture was then heated and an azeotrope toluene/EtOH/water was distilled around 70 °C. After 3 *h the*

solution was evaporated giving a thick reddish oil (1.7 g) which contained toluene as the only impurity (^{1}H NMR). To this residue 4N NaOH (10 mL) was added and the solution was heated to 110 °C for 2 h. After cooling to rt the aqueous phase was extracted with CH_2Cl_2 (2x10 mL), and the organic phase was washed with brine (10 mL). The pooled aqueous phase was cooled at 5 °C, then HCl (20% w/v, around 6 mL) was added until pH 4.5. The solid obtained was filtered and washed with water, dried in the oven at 45 °C at reduced pressure yielding **28** as a white solid, m.p. 170-171 °C (830 mg, 2.60 mmoles, 55.5%).

A solution of **28** (830 mg, 2.60 mmoles) in abs. EtOH (1 mL) and 20% v/v H_2SO_4 (7 mL) was stirred at 75 °C for 1.5 h. After cooling at rt the mixture was poured into crushed ice (10 mL). Solid $NaHCO_3$ was added portionwise (T<10 °C) until pH 9 (around 7 g). The solid formed was filtered off and washed with water (2 mL). The aqueous phase was extracted with AcOEt (3x10 mL), then the organic phase was dried (Na_2SO_4) and evaporated. Recrystallization from AcOEt producied 3-phenyl-1H-imidazo[1,2-b]pyrazole **3** as white crystals, m.p. 183 °C (390 mg, 2.12 mmoles, 81.5%). R_f 0.47 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 72.01; H, 5.03; N, 22.85, calculated for $C_{11}H_9N_3$ C, 72.11; H, 4.95; N, 22.94%; υ(cm^{-1}) 3150 (NH); δ_H($CDCl_3$), 5.95 (s,1H,2-H), 7.15-7.35 (m,6H,Arom. and 7-H), 7.60 (d,1H,6-H), 11.05 (b,1H,NH).

7-Ethoxycarbonyl-1H-imidazo[1,2-b]pyrazole ***4***.- 1,4,5-trisubstituted pyrazole **29** was prepared from **19** and **20** as seen for compound **1**. A solution of **29** (20 g, 73.7 mmoles) in abs. EtOH (20 mL) and 20% v/v H_2SO_4 (140 mL) was refluxed for 1 h, then after cooling to rt it was poured into crushed ice (200 g) and

the pH was brought to 8 with solid $NaHCO_3$. Extraction with CH_2Cl_2 (3x400 mL), washing with brine, drying (Na_2SO_4) and concentration to dryness produced a solid residue. Recrystallization from AcOEt afforded 7-ethoxycarbonyl-1H-imidazo[1,2-b]pyrazole **4** as a pale yellow solid, m.p. 131 °C (8.68 g, 58.9 mmoles, 80.0%). R_f 0.36 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 53.51; H, 5.11; N, 23.38, calculated for $C_8H_9N_3O_2$ C, 53.63; H, 5.06; N, 23.45%; $\upsilon(cm^{-1})$ 3150 (NH), 1675 (COO); $\delta_H(CDCl_3)$ 1.40 (t,3H,CH_3), 4.30 (q,2H,CH_2), 7.15 (d,1H,2-H), 7.45 (d,1H,3-H), 8.05 (s,1H,6-H), 10.50 (b,1H,NH).

7-methyl-1H-imidazo[1,2-b]pyrazole **5**.- A solution of **4** (180 mg, 1 mmole) in dry THF (0.8 mL) was added to a suspension of $LiAlH_4$ (114 mg, 3 mmoles) in dry THF (1.5 mL). After heating at 60 °C for 1 h and cooling to rt AcOEt (25 mL) and water (10 mL) were added. The solution was neutralized (AcOH) and the aqueous phase was extracted (AcOEt). The pooled organic phase was dried (Na_2SO_4) and concentrated to give 7-methyl-1H-imidazo[1,2-b]pyrazole **5** as a white solid, m.p. 200-202 °C (115 mg, 0.95 mmoles, 95%). R_f 0.45 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 59.35; H, 5.91; N, 34.54, calculated for $C_6H_7N_3$ C, 59.49; H, 5.82; N, 34.69%; $\upsilon(cm^{-1})$ 3145 (NH); $\delta_H(CDCl_3)$ 2.45 (s,3H,CH_3), 6.90 (d,1H,2-H), 7.30 (d,1H,3-H), 7.45 (s,1H,6-H), 10.85 (b,1H,NH).

7-carboxy-1H-imidazo[1,2-b]pyrazole hydrochloride **6**.- Compound **21** (12.2 g, 50.0 mmoles) was dissolved in dry dioxane (120 mL). Ethereal HCl (3.1% w/v, 150 mL) was added dropwise under stirring in 1 h, while a precipitate formed. After 28 h the solvent was decanted and the gummy residue stirred for 18 h with

fresh dioxane (370 mL). The resulting solid was filtered, washed with Et_2O and dried affording **6** as white crystals, m.p.115 °C dec. (9.0 g, 48.0 mmoles, 96.0%). Microanalysis: found C, 38.20; H, 3.41; N, 22.18, calculated for $C_6H_5N_3O_2$.HCl C, 38.42; H, 3.22; N, 22.40%; $\upsilon(cm^{-1})$ 3130 (NH), 1680 (COOH); $\delta_H(d_6\text{-DMSO})$ 7.30 (d,1H,2-H), 7.70 (d,1H,3-H), 7.90 (s,1H,6-H), 9.70 (s,2H,NH_2), 12.10 (s,1H,OH).

7-(N,N-Dimethylcarboxamido)-1H-imidazo[1,2-b]pyrazole ***7b***.- A solution of **21** (30 g, 123 mmoles) and carbonyldiimidazole (37.32 g, 173 mmoles) in dry THF (200 mL) was stirred for 2 h, then the solvent was evaporated. The residue was dissolved in water (200 mL) and the mixture was extracted with CH_2Cl_2 (3x200 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated to give **30** as an oil (28 g, 95.3 mmoles, 77.5%).

To a solution of **30** (14.67 g, 50 mmoles) in dry THF (100 mL) dimethylamine (40% in water, 28.2 mL, 250 mmoles) was added dropwise. Stirring was continued for 2.5 h, then the mixture was concentrated and the residue taken up with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ solution, with water and then dried (Na_2SO_4). After concentration the residue (16.4 g) was chromatographed on silica gel (AcOEt) giving **31b** as a solid, m.p. 68 °C (13.2 g, 48.8 mmoles, 97.5%).

A solution of **31b** (13.2 g, 48.8 mmoles) in abs. EtOH (13 mL) and 1N H_2SO_4 (91 mL) was refluxed for 1 h. After cooling to rt and taking the pH to 8 with solid $NaHCO_3$, the mixture was extracted with AcOEt (3x100 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated to give a residue (7.8 g) which was crystallized from water/EtOH to afford pure 7-(N,N-

dimethylcarboxamido)-1H-imidazo[1,2-b]pyrazole **7b** as white crystals, m.p. 256-7 °C dec. (5.3 g, 29.7 mmoles, 61.0%). R_f 0.50 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 53.80; H, 5.71; N, 31.33, calculated for $C_8H_{10}N_4O$ C, 53.92; H, 5.66; N, 31.44%; $\upsilon(cm^{-1})$ 3360 (NH), 1615 (CON); $\delta_H(CDCl_3)$ 3.20 (s,6H,CH_3), 6.95 (d,1H,2-H), 7.20 (d,1H,3-H), 7.95 (s,1H,6-H), 10.15 (b,1H,NH).

*Compounds **7a,c**.*- These compounds were prepared as described for **7b**. **7a:** (white crystals, m.p. 205-206 °C). R_f 0.47 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 54.40; H, 5.62; N, 25.29, calculated for $C_{10}H_{12}N_4O_2$ C, 54.54; H, 5.49; N, 25.44%; $\upsilon(cm^{-1})$ 3320 (NH), 1625 (CON); $\delta_H(CDCl_3)$ 3.55 (t,4H,CH_2-N), 4.45 (t,4H,CH_2-O), 6.85 (d,1H,2-H), 7.30 (d,1H,3-H), 7.80 (s,1H,6-H), 10.55 (b,1H,NH). **7c:** (white crystals, m.p. 115-117 °C). R_f 0.40 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 54.17; H, 6.92; N, 31.55, calculated for $C_{10}H_{15}N_5O$ C, 54.28; H, 6.83; N, 31.65%; $\upsilon(cm^{-1})$ 3270 (NH), 1630 (CON); $\delta_H(CDCl_3)$ 2.50 (s,6H,CH_3), 2.85 (t,2H,CH_2-N), 3.50 (m,2H,CH_2-NHCO), 7.00 (d,1H,2-H), 7.30 (d,1H,3-H), 8.00 (s,1H,6-H), 10.70 (b,1H,NH).

*7-(3-Pyridylmethoxycarbonyl)-1H-imidazo[1,2-b]pyrazole **8c**.*- A solution of 3-pyridinemethanol (3.71 g, 34 mmoles) in dry THF (35 mL) was cooled to 0 °C. NaH (50% in mineral oil, 1.62 g, 34 mmoles) was added cautiously, and when gas evolution ceased a cooled solution of **30** (10 g, 34 mmoles) in dry THF (35 mL) was added dropwise (T<5 °C). After stirring for 10 minutes water (150 mL) was cautiously added and the mixture was extracted with CH_2Cl_2 (3x100 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give pure **32c** as an oil (10.80 g, 34 mmoles, 100%).

A solution of **32c** (10.72 g, 34 mmoles) in abs. EtOH (11 mL) and 20% v/v H_2SO_4 (75 mL) was refluxed for 30 minutes. After cooling at rt it was poured into crushed ice (100 g) and the pH brought to 8 with solid $NaHCO_3$, then to 9 with 4N NaOH. The mixture was extracted with AcOEt (3x200 mL), the organic phase was washed with brine, dried (Na_2SO_4) and concentrated to give a solid residue (9 g). Chromatography on silicagel (CH_2Cl_2/MeOH 9/1) afforded 7-(3-pyridylmethoxycarbonyl)-1H-imidazo[1,2-b]pyrazole **7c** as a white solid, m.p. 182 °C (5.9 g, 26.5 mmoles, 78.0%). R_f 0.32 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 59.39; H, 4.30; N, 23.00, calculated for $C_{12}H_{10}N_4O_2$ C, 59.50; H, 4.16; N, 23.13%; $\upsilon(cm^{-1})$ 3155 (NH), 1700 (COO); $\delta_H(CDCl_3)$ 5.40 (s,2H,CH_2O), 7.35-7.40 (M,2H,5-Py and 2-H), 7.80-7.90 (M,2H,4-Py and 3-H), 8.05 (s,1H,6-H), 8.55 (d,1H,6-Py), 8.70 (s,1H,2-Py), 11.10 (b,1H,NH).

*Compounds **8a,b,d-h**.* These compounds were prepared as seen for **8c**. **8a:** (white solid, m.p. 106 °C). R_f 0.32 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 53.96; H, 6.43; N, 25.09, calculated for $C_{10}H_{14}N_4O_2$ C, 54.04; H, 6.35; N, 25.21%; $\upsilon(cm^{-1})$ 3160, 3130 (NH), 1680 (COO); $\delta_H(CDCl_3)$ 2.40 (s,6H,CH_3), 2.75 (t,2H,CH_2N), 4.35 (t,2H,CH_2O), 6.90 (d,1H,2-H), 7.20 (d,1H,3-H), 7.80 (s,1H,6-H), 11.25 (b,1H,NH). **8b:** (white solid, m.p. 90 °C). R_f 0.34 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 59.39; H, 7.05; N, 21.19, calculated for $C_{13}H_{18}N_4O_2$ C, 59.53; H, 6.92; N, 21.36%; $\upsilon(cm^{-1})$ 3145 (NH), 1695 (COO); $\delta_H(CDCl_3)$ 1.40-1.60 (m,6H,CH_2-CH_2), 2.75-2.85 (m,6H,CH_2N), 4.40 (t,2H,CH_2O), 6.90 (d,1H,2-H), 7.30 (d,1H,3-H), 7.90 (s,1H,6-H), 10.95 (s,1H,NH). **8d:** (white crystals, m.p. 166 °C). R_f 0.34 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 50.77; H, 5.18; N, 23.63,

calculated for $C_{10}H_{12}N_4O_3$ C, 50.84; H, 5.12; N, 23.72%; $\upsilon(cm^{-1})$ 3165, 3140 (NH), 1680 (COO), 1635 (CON); $\delta_H(CDCl_3)$ 2.50 (s,3H,CH_3), 3.25 (m,2H,CH_2N), 4.45 (t,2H,CH_2O), 7.40 (d,1H,2-H), 7.80 (d,1H,3-H), 8.00 (s,1H,6-H), 11.00 (b,1H,NH). **8e:** (yellow solid, m.p. 92-93 °C). R_f 0.39 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 54.39; H, 6.24; N, 21.08, calculated for $C_{12}H_{16}N_4O_3$ C, 54.54; H, 6.10; N, 21.20%; $\upsilon(cm^{-1})$ 3160 (NH), 1705 (COO); $\delta_H(CDCl_3)$ 2.85 (t,2H,CH_2N), 3.00 (t,4H,CH_2N), 4.15 (t,4H,CH_2O), 4.40 (t,2H,CH_2OCO), 7.35 (d,1H,2-H), 7.80 (d,1H,3-H), 8.00 (s,1H,6-H), 10.90 (b,1H,NH). **8f:** (white solid, m.p. 90-91 °C). R_f 0.35 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 57.99; H, 6.54; N, 22.50, calculated for $C_{12}H_{16}N_4O_2$ C, 58.05; H, 6.50; N, 22.57%; $\upsilon(cm^{-1})$ 3130 (NH), 1675 (COO); $\delta_H(CDCl_3)$ 1.45-1.65 (m,4H,CH_2-CH_2), 2.80-2.90 (m,6H,CH_2N), 4.30 (t,2H,CH_2O), 7.40 (d,1H,2-H), 7.75 (d,1H,3-H), 7.95 (s,1H,6-H), 11.05 (b,1H,NH). **8g:** (white crystals, m.p. 165-166 °C). R_f 0.30 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 56.19; H, 7.04; N, 25.08, calculated for $C_{13}H_{19}N_5O_2$ C, 56.30; H, 6.91; N, 25.25%; $\upsilon(cm^{-1})$ 3165 (NH), 1695 (COO); $\delta_H(CDCl_3)$ 2.45 (s,3H,CH_3), 2.80-3.00 (m,10H,CH_2N), 4.40 (t,2H,CH_2O), 7.35 (d,1H,2-H), 7.75 (d,1H,3-H), 7.95 (s,1H,6-H), 11.10 (b,1H,NH). **8h:** (white solid, m.p. 76 °C). R_f 0.38 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 57.52; H, 7.32; N, 22.23, calculated for $C_{12}H_{18}N_4O_2$ C, 57.58; H, 7.25; N, 22.38%; $\upsilon(cm^{-1})$ 3160 (NH), 1685 (COO); $\delta_H(CDCl_3)$ 1.40 (t,6H,CH_3), 2.65 (q,4H,CH_2.CH_3), 2.80 (t,2H,CH_2N), 4.35 (t,2H,CH_2O), 6.85 (d,1H,2-H), 7.35 (d,1H,3-H), 7.95 (s,1H,6-H), 10.80 (b,1H,NH).

Methyl 1H-imidazo[1,2-b]pyrazol-7-yl carbamate ***9a***.- $N_2H_4.H_2O$ (350 mL, 7 moles) was added dropwise to a solution of **29** (70 g, 258 mmoles) in abs. EtOH (70 mL). After refluxing for 16 h the mixture was cooled to rt, brine (100 mL) was added and the solution was extracted with $CHCl_3$ (3 x 300 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated affording **33** as an oil (60.7 g, 236 mmoles, 91.5%).

A solution of **33** (60.7 g, 236 mmoles) in trifluoroacetic acid (500 mL) was stirred at rt for 6 h. After concentration of the solvent the residue was dissolved in EtOH (500 mL) and concentrated. The residue was dissolved in water, andthe pH brought to 8 with solid $NaHCO_3$ while a precipitate was formed. The solid was filtered and recrystallized from EtOH/water to give **34** as a pale orange solid, m.p. 177 °C dec. (32.6 g, 197 mmoles, 83.5%).

A solution of **34** (22 g, 133 mmoles) in water (275 mL) and 20% HCl (150 mL) was cooled at 0 °C and Et_2O (1000 mL) was added. A solution of $NaNO_2$ (9.2 g, 133 mmoles) in water (92 mL) was added dropwise (T<5 °C). Vigorous stirring was continued for 15 minutes, then the organic phase was separated, dried (Na_2SO_4) and concentrated to give **35** as a crude brown solid which was used without further purification (19.5 g, 111 mmoles, 83.0%).

A solution of **35** (19.5 g, 111 mmoles) in MeOH (200 mL) and toluene (200 mL) was refluxed for 67 h. After evaporation the residue (5.9 g) was chromatographed on silica gel (CH_2Cl_2/MeOH 9/1) to give methyl 1H-imidazo[1,2-b]pyrazol-7-yl carbamate **9a** as a white solid, m.p. 185 °C (2.0 g, 11.1 mmoles, 10.0%). R_f 0.33 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 46.59; H,

4.59; N, 30.95, calculated for $C_7H_8N_4O_2$ C, 46.67; H, 4.48; N, 31.10%; $\upsilon(cm^{-1})$ 3250 (NH), 1700 (OCONH); $\delta_H(CDCl_3)$ 3.60 (s,3H,CH_3), 7.25 (d,1H,2-H), 7.40 (d,1H,3-H), 7.65 (s,1H,6-H), 8.90 (s,1H,NHCO), 10.95 (b,1H,NH).

*Compound **9b**.*- Compound **9b** was prepared as described for **9a. 9b:** (white crystals, m.p. 194 °C). R_f 0.38 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 49.39; H, 5.28; N, 28.70, calculated for $C_8H_{10}N_4O_2$ C, 49.48; H, 5.19; N, 28.85%; $\upsilon(cm^{-1})$ 3255 (NH), 1700 (OCONH); $\delta_H(CDCl_3)$ 1.45 (t,3H,CH_3), 4.50 (q,2H,CH_2), 7.30 (d,1H,2-H), 7.50 (d,1H,3-H), 7.70 (s,1H,6-H), 8.95 (s,1H,NHCO), 11.10 (b,1H,NH).

*7-Phenyl-1H-imidazo[1,2-b]pyrazole **10**.*- Compound **19** (3.71 g, 25.0 mmoles) was added dropwise under stirring at rt to a solution of **36** (3.63 g, 25.0 mmoles) in abs. EtOH (50 mL). The solution was refluxed for 2 h, then after cooling at rt the solvent was concentrated. The solid residue obtained was chromatographed on silica gel with AcOEt/*n*-heptane 1/1 to give **37** as an oil (5.75 g, 20.9 mmoles, 83.5%).

A solution of **37** (5.75 g, 20.9 mmoles) in abs. EtOH (20 mL) and 20% v/v H_2SO_4 (140 mL) was refluxed for 1 h, then after cooling at rt it was poured into crushed ice (200 g) and the pH was brought to 8 with solid $NaHCO_3$. Extraction with CH_2Cl_2 (3x400 mL), washing with brine, drying (Na_2SO_4) and concentration produced a solid residue. Recrystallization from AcOEt/*n*-heptane afforded 7-phenyl-1H-imidazo[1,2-b]pyrazole **10** as white crystals, m.p. 214-215 °C, lit. 212-214 °C[17] (2.78 g, 15.2 mmoles, 72.5%). R_f 0.49 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 71.95; H, 5.07; N, 22.81, calculated for $C_{11}H_9N_3$ C, 72.11; H,

4.95; N, 22.94%; $\upsilon(cm^{-1})$ 3155 (NH); $\delta_H(CDCl_3)$, 5.95 (d,1H,2-H), 7.20-7.45 (m,6H,Arom. and 3-H), 7.65 (d,1H,6-H), 11.40 (b,1H,NH).

6-Methyl-1H-imidazo[1,2-b]pyrazole hydrochloride ***11***.- A solution of **19** (9.02 g, 60.82 mmoles) and **38** (5.0 g, 60.82 mmoles) in abs. EtOH (18 mL) was refluxed for 20 h. The solution was then cooled to rt, the solvent was evaporated and the crude distilled to give **39** as a pale yellow oil, eb. p. 110-120 °C/ 10 mm Hg (11.5 g, 53.9 mmoles, 86.5%).

A solution of **39** (11.0 g, 51.6 mmoles) in abs. EtOH (448 mL) and 20% v/v H_2SO_4 (112 mL) was refluxed for 4.5 h. After cooling to rt the pH was brought to 7 with solid $NaHCO_3$, the suspension was concentrated and the residue taken up with brine and extracted with AcOEt (2x100 mL). The organic phase was dried (Na_2SO_4) and concentrated to give 6-methyl-1H-imidazo[1,2-b]pyrazole **11** as a white solid, m.p. 177 -178 °C, lit. m.p. 178-179 °C[4] (4.58 g, 37.8 mmoles, 73.5%) R_f 0.45 ($CHCl_3$/MeOH 95/5); microanalysis: found C, 59.38; H, 5.89; N, 34.58, calculated for $C_6H_7N_3$ C, 59.49; H, 5.82; N, 34.69%; $\upsilon(cm^{-1})$ 3115 (NH); $\delta_H(CDCl_3)$, 2.35 (s,3H,CH_3), 5.40 (s,1H,7-H), 6.95 (d,1H,2-H), 7.35 (d,1H,3-H), 11.00 (b,1H,NH).

6-Ethoxycarbonyl-1H-imidazo[1,2-b]pyrazole hydrochloride ***12***.- A solution of **19** (14.81 g, 100 mmoles) in water (150 mL) and 20% v/v H_2SO_4 (23.1 mL, 100 mmoles) was added dropwise under vigorous stirring to a solution of **40** (16.31 g, 100 mmoles) in $CHCl_3$ (150 mL). Stirring at rt was continued for 72 h. The organic phase was washed with sat. $NaHCO_3$, dried (Na_2SO_4) and

concentrated. The oily residue was chromatographed on silica gel (AcOEt/*n*-heptane 7/3) to give **41** as a white solid, m.p. 75 °C (18.7 g, 69 mmoles, 69%).

An ethereal HCl solution (2.6% w/v, 400 mL) was added in 30 minutes to a solution of **41** (18 g, 66 mmoles) in dry THF (350 mL). After stirring at rt for 2 h the suspension was filtered and the solid was washed with Et_2O. The solid was then suspended in water (250 mL), treated with solid $NaHCO_3$ and extracted with AcOEt (4x200 mL). After drying (Na_2SO_4) and concentration the residue was chromatographed on silicagel ($CHCl_3$/MeOH 9/1) producing 6-ethoxycarbonyl-1H-imidazo[1,2-b]pyrazole **12** as a white solid. Recrystallization (AcOEt/*n*-heptane) gave pure **12** as white crystals, m.p. 160 °C (5.12 g, 28.6 mmoles, 43.5%). R_f 0.42 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 53.55; H, 5.08; N, 23.41, calculated for $C_8H_9N_3O_2$ C, 53.63; H, 5.06; N, 23.45%; $\upsilon(cm^{-1})$ 3165 (NH), 1715 (COO); $\delta_H(CDCl_3)$, 1.30 (t,3H,CH_3), 4.30 (q,2H,CH_2), 6.25 (s,1H,7-H), 7.40 (d,1H,2-H), 7.65 (d,1H,3-H), 11.35 (b,1H,NH).

6-Carboxy-1H-imidazo[1,2-b]pyrazole hydrochloride ***13***.- A suspension of **12** (7.5 g, 42 mmoles) in 4N NaOH (70 mL) was stirred at rt for 1 h. The resulting solution was washed with CH_2Cl_2 (2x250 mL). The aqueous phase was acidified with 20% HCl until pH 4 in an ice bath (T<30 °C) and the precipitate was filtered, washed with Et_2O and dried producing 7-carboxy-1H-imidazo[1,2-b]pyrazole **13** as white crystals, m.p. 230 °C dec. (3.7 g, 24.5 mmoles, 58.5%). R_f 0.16 ($CHCl_3$/MeOH 9/1); microanalysis: found C, 47.60; H, 3.41; N, 27.73, calculated for $C_6H_5N_3O_2$ C, 47.69; H, 3.33; N, 27.81%; $\upsilon(cm^{-1})$ 1670 (COOH); $\delta_H(CDCl_3)$, 6.20

(s,1H,7-H), 7.35 (d,1H,2-H), 7.65 (d,1H,3-H), 11.40 (b,1H,NH), 12.30 (b,1H,COOH).

6-Acetylamino-1H-imidazo[1,2-b]pyrazole hydrochloride ***14a***.- Compound **42** (65 g, 281 mmoles) was dissolved at 0 °C in a separatory funnel into a sat. K_2CO_3 solution, and the mixture was rapidly extracted with Et_2O (3x300 mL). The organic layer was dried (K_2CO_3) and concentrated at rt. The oily residue was added dropwise to a solution of **19** (50 g, 337 mmoles) in abs. EtOH (200 mL) at 50 °C and stirring was continued for 1 h. The mixture was evaporated and the residue dissolved in CH_2Cl_2 (250 mL), washed with sat. $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue (47.5 g) was chromatographed on silica gel ($CHCl_3$/MeOH 95/5) to give **43** as an oil (28 g, 131 mmoles, 46.5%).

A solution of **43** (20 g, 93.4 mmoles) in CH_2Cl_2 (250 mL) was cooled at 0 °C, TEA (14.1 g, 140 mmoles) and acetic anhydride (9.52 g, 93.4 mmoles) were added and stirring at 0 °C was continued for 3 h. The mixture was washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated to give **44a** as an oil (19.8 g, 77.3 mmoles, 82.5%).

Ethereal HCl (2.5% w/v, 200 mL) was added to a solution of **44a** (13.5 g, 52.7 mmoles) in dry THF. After stirring at rt for 48 h, the precipitate was filtered, washed with Et_2O and dried to give 6-acetylamino-1H-imidazo[1,2-b]pyrazole **14a** as yellow crystals, m.p. 240 °C dec. (7.72 g, 47.0 mmoles, 89.0%). Microanalysis: found C, 41.74; H, 4.70; N, 27.74, calculated for $C_7H_8N_4O.HCl$ C, 41.91; H, 4.52; N, 27.93%; $\upsilon(cm^{-1})$ 3100 (NH), 1680 (CONH); $\delta_H(d_6\text{-DMSO})$ 2.20 (s,3H,CH_3), 6.15

(s,1H,7-H), 7.40 (d,1H,2-H), 7.65 (d,1H,3-H), 11.35 (s,1H,NH), 12.20 (b,1H,HCl).

*Compound **14b**.*- Compound **14b** was prepared as described for **14a. 14b** (pale yellow crystals, m.p. 225-226 °C dec). Microanalysis: found C, 63.51; H, 4.65; N, 24.58, calculated for $C_{12}H_{10}N_4O$ C, 63.71; H, 4.46; N, 24.76%; $\upsilon(cm^{-1})$ 3145 (NH), 1670 (CONH); $\delta_H(d_6\text{-DMSO})$ 6.20 (s,1H,7-H), 7.15 (d,1H,2-H), 7.50 (m,6H,5Ar and 3-H), 11.20 (s,1H,NH), 12.45 (b,1H,HCl).

*6-(4-Chlorophenyl)-1H-imidazo[1,2-b]pyrazole **15b**.*- MeCN (8 mL, 152 mmoles) was added dropwise to a suspension of **45b** (11 g, 64.5 mmoles) and 50% NaH (7.2 g, 150 mmoles) in toluene under stirring at 90 °C. After 24 h the mixture was cooled at rt, the precipitate was filtered and washed with toluene. The solid was then dissolved in water and the pH was brought to 5 with 10% w/v HCl, then the suspension was extracted with CH_2Cl_2 (4x250 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give **46b** as a solid, m.p. 129 °C (7.83 g, 43.6 mmoles, 67.5%).

A solution of **19** (6.9 g, 46.6 mmoles) and **46b** (7.0 g, 39.0 mmoles) in abs. EtOH was refluxed for 30 min. After cooling at rt the solvent was concentrated and the residue dissolved in AcOEt (250 mL), washed with sat. $NaHCO_3$ and brine, then dried (Na_2SO_4) and concentrated to give **47b** as a solid, m.p. 70 °C (10.11 g, 32.6 mmoles, 83.5%).

A solution of **47b** (10 g, 32.3 mmoles) in abs. EtOH (10 mL) and 20% v/v H_2SO_4 (70 mL) was refluxed for 20 minutes. After cooling to rt the solution was diluted with water (100 mL), pH brought to 8 with solid $NaHCO_3$ and extracted

with CH_2Cl_2 (3x100 mL). The organic layer was dried (Na_2SO_4), concentrated and the residue crystallized from AcOEt/*n*-heptane to afford pure **15b** as white crystals, m.p. 204-205 °C, lit. 203-205 °C[17] (3.76 g, 17.3 mmoles, 53.5%). R_f 0.26 (AcOEt/*n*-heptane 1/1); microanalysis: found C, 54.28; H, 6.38; Cl(org) 16.12; N, 20.98, calculated for $C_{11}H_8ClN_3$ C, 60.70; H, 3.70; Cl(org) 16.29; N, 19.31%; $\upsilon(cm^{-1})$ 3150 (NH); $\delta_H(CDCl_3)$ 5.90 (s,1H,7-H), 6.75 (d,1H,2-H), 7.20 (d,1H,3-H), 7.30 (d,2H,Arom.), 7.65 (d,2H,Arom.), 10.95 (b,1H,NH).

*Compounds **15a,c-j**.*- Compounds **15a,c-j** were prepared as described for **15b. 15a:** (white solid, m.p. 185-186 °C, lit. 187-189 °C[17]). R_f 0.34 (AcOEt/*n*-heptane 2/1); microanalysis: found C, 72.00; H, 5.02; N, 22.83, calculated for $C_{11}H_9N_3$ C, 72.11; H, 4.95; N, 22.94%; $\upsilon(cm^{-1})$ 3140 (NH); $\delta_H(CDCl_3)$ 6.00 (s,1H,7-H), 6.85 (d,1H,2-H), 7.20-7.40 (m,6H,Arom. and 3-H), 11.30 (b,1H,NH). **15c:** (white solid, m.p. 179-180 °C). R_f 0.35 (AcOEt/*n*-heptane 1/1); microanalysis: found C, 52.34; H, 2.89; Cl(org) 28.09; N, 16.60, calculated for $C_{11}H_7Cl_2N_3$ C, 52.41; H, 2.80; Cl(org) 28.23; N, 16.67%; $\upsilon(cm^{-1})$ 3165 (NH); $\delta_H(CDCl_3)$ 6.25 (s,1H,7-H), 6.90 (d,1H,2-H), 7.30-7.35 (m,2H,Arom. and 3-H), 7.65 (d,1H,Arom.), 7.85 (s,1H,Arom.), 11.05 (b,1H,NH). **15d:** (white solid, m.p. 199-200 °C, lit. 197-200 °C[17]). R_f 0.30 (AcOEt/*n*-heptane 1/1); microanalysis: found C, 72.99; H, 5.71; N, 21.18, calculated for $C_{12}H_{11}N_3$ C, 73.07; H, 5.62; N, 21.30%; $\upsilon(cm^{-1})$ 3125 (NH); $\delta_H(CDCl_3)$ 2.05 (s,3H,CH_3), 6.00 (s,1H,7-H), 6.85 (d,1H,2-H), 7.25-7.35 (m,5H,Arom. and 3-H), 10.75 (b,1H,NH). **15e:** (white solid, m.p. 204-205 °C, lit. 201-204 °C[17]). R_f 0.23 (AcOEt/*n*-heptane 1/1); microanalysis: found C, 67.45; H,

5.34; N, 19.59, calculated for $C_{12}H_{11}N_3O$ C, 67.59; H, 5.20; N, 19.71%; $\upsilon(cm^{-1})$ 3145 (NH); $\delta_H(CDCl_3)$ 3.95 (s,3H,CH_3), 5.95 (s,1H,7-H), 6.85 (d,1H,2-H), 7.15-7.30 (m,5H,Arom. and 3-H), 10.90 (b,1H,NH). **15f:** (pale yellow solid, m.p. 139-140 °C, lit. 134-135 °C[17]). R_f 0.30 (AcOEt/*n*-heptane 1/2); microanalysis: found C, 57.25; H, 3.33; F, 22.45; N, 16.59, calculated for $C_{12}H_8F_3N_3$ C, 57.37; H, 3.21; F, 22.69; N, 16.73%; $\upsilon(cm^{-1})$ 3160 (NH); $\delta_H(CDCl_3)$ 6.10 (s,1H,7-H), 6.90 (d,1H,2-H), 7.35-7.45 (m,5H,Arom. and 3-H), 7.75 (d,2H,Arom.), 10.75 (b,1H,NH). **15g:** (white solid, m.p. 205-206 °C). R_f 0.32 (AcOEt/*n*-heptane 1/1); microanalysis: found C, 65.81; H, 5.21; N, 16.39, calculated for $C_{14}H_{13}N_3O_2$ C, 65.87; H, 5.13; N, 16.46%; $\upsilon(cm^{-1})$ 3145 (NH), 1715 (COO); $\delta_H(CDCl_3)$ 1.40 (t,3H,CH_3), 4.30 (q,2H,CH_2), 6.05 (s,1H,7-H), 6.85 (d,1H,2-H), 7.25 (d,1H,3-H), 7.40 (d,2H,Arom.), 7.80 (d,2H,Arom.), 11.45 (b,1H,NH). **15h:** (white solid, m.p. 213-214 °C). R_f 0.31 (AcOEt/*n*-heptane 2/1); microanalysis: found C, 61.39; H, 5.65; N, 15.22, calculated for $C_{14}H_{15}N_3O_3$ C, 61.53; H, 5.53; N, 15.38%; anal $C_{14}H_{15}N_3O_3$ (C, H, N); $\upsilon(cm^{-1})$ 3160 (NH); $\delta_H(CDCl_3)$ 3.90 (s,3H,CH_3), 3.85 (s,6H,CH3), 5.90 (s,1H,7-H), 6.70 (d,1H,2-H), 7.00 (s,2H,Arom.), 7.10 (d,1H,3-H), 11.05 (b,1H,NH). **15i:** (yellow solid, m.p. 207-208 °C, lit. 205-208 °C[17]). R_f 0.26 (AcOEt/*n*-heptane 2/1); microanalysis: found C, 65.14; H, 4.45; N, 30.29, calculated for $C_{10}H_8N_4$ C, 65.21; H, 4.38; N, 30.42%; $\upsilon(cm^{-1})$ 3165 (NH); $\delta_H(CDCl_3)$ 6.10 (s,1H,7-H), 6.80 (d,1H,2-H), 7.20-7.40 (m,5H,Arom. and 3-H), 11.00 (b,1H,NH). **15j:** (white solid, m.p. 146-147 °C, lit. 147-149 °C[17]). R_f 0.39 (AcOEt/*n*-heptane 2/1); microanalysis: found C, 73.00; H, 5.69; N, 21.18, calculated for $C_{12}H_{11}N_3$ C,

73.07; H, 5.62; N, 21.30%; $\upsilon(cm^{-1})$ 3145 (NH); $\delta_H(CDCl_3)$ 2.85 (q,2H,CH_2), 5.70 (s,1H,7-H), 6.70 (d,1H,2-H), 7.20-7.35 (m,6H,Arom. and 3-H), 10.95 (b,1H,NH). **15k:** (white crystals, m.p. 229-230 °C). R_f 0.16 (AcOEt/*n*-heptane 1/1); microanalysis: found C, 63.39; H, 4.05; N, 18.41, calculated for $C_{12}H_9N_3O_2$ C, 63.43; H, 3.99; N, 18.49%; $\upsilon(cm^{-1})$ 3140 (NH), 1690 (COO); $\delta_H(CDCl_3)$ 6.30 (s,1H,7-H), 7.25 (d,1H,2-H), 7.45-7.60 (m,3H,Arom. and 3-H), 7.85 (d,2H,Arom.), 11.30 (b,1H,NH).

2,3-diphenyl-1H-imidazo[1,2-b]pyrazole ***16***.- A suspension of **22** (4.4 g, 53.0 mmoles) and **48** (11.25 g, 53.0 mmoles) in tetraline (300 mL) was stirred at 240 °C for 48 h, then after cooling to rt the solvent was concentrated (15 mm Hg). The residue was chromatographed on silicagel ($CHCl_3$/MeOH 98/2) affording **49** as a solid, m.p. 147 °C (8.72 g, 31.6 mmoles, 59.5%).

A suspension of **49** (8.00 g, 28.8 mmoles) in quinoline (100 mL) was refluxed for 6 h, then after cooling to rt the solvent was distilled off at 105 °C at reduced pressure (15 mm Hg). The residue was chromatographed on silicagel (CH_2Cl_2/MeOH 95/5) to give a solid which was crystallized from Et_2O/light petroleum to afford **16** as a white solid, m.p. 154 °C (1.15 g, 4.43 mmoles, 15.5%). R_f 0.63 (CH_2Cl_2/MeOH 95/5); microanalysis: found C, 78.59; H, 5.18; N, 16.08, calculated for $C_{17}H_{13}N_3$ C, 78.74; H, 5.05; N, 16.20%; $\upsilon(cm^{-1})$ 3300 (NH); $\delta_H(CDCl_3)$ 6.20 (d,1H,7-H), 7.30-7.90 (m,11H,Arom. and 6-H), 12.55 (b,1H,NH).

7-cyano, 6-cyanomethyl-1H-imidazo[1,2-b]pyrazole ***17***.- To a solution of **51** (1.32 g, 10.0 mmoles) in abs. EtOH (13 mL) compound **19** (1.78 g, 12.0

mmoles) was added dropwise under stirring at reflux. After refluxing for 11 h the solvent was evaporated and the residue was washed with *n*-hexane and AcOEt, then dried to give a crude orange brown solid used without further purification (1.15 g, 4.37 mmoles, 43.5%).

A solution of **52** (150 mg, 0.57 mmoles) in abs. EtOH (5.2 mL) and 20% v/v H_2SO_4 (1.3 mL) was refluxed for 1 h, then after cooling the pH was brought to 8 with solid $NaHCO_3$. After concentration the residue was taken up with water (20 mL) and extracted with AcOEt (5x25 mL). The organic phase was dried (Na_2SO_4) and concentrated to give **17** as a solid, m.p. 117 °C (94 mg, 0.55 mmoles, 96.5%). R_f 0.31 (EtOAc/*n*-heptane 1/1); microanalysis: found C, 56.09; H, 3.02; N, 40.83, calculated for $C_8H_5N_5$ C, 56.14; H, 2.94; N, 40.92%; $\upsilon(cm^{-1})$ 3150 (NH) 2270 (CN); $\delta_H(CDCl_3)$ 3.05 (s,2H,CH_2), 6.70 (d,1H,2-H), 7.30 (d,1H,3-H).

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