PREPARATIVE SCALE CONVERSION OF D-XYLOSE INTO HYDROPHILICALLY FUNCTIONALIZED PYRAZOLES[1]

Volker Diehl, Eckehard Cuny, and Frieder W. Lichtenthaler*

Institut für Organische Chemie, Technische Universität Darmstadt,

D-64287 Darmstadt, Germany

Abstract – An expeditious, 4-step procedure is described for the conversion of bulk-scale accessible D-xylose into 5-hydroxymethyl-1-phenylpyrazole-3-carboxaldehyde (**3**), which, in turn, is converted into various pyrazole building blocks with versatile application profiles, such as the 1-phenylpyrazole-3,5-dicarboxylic acid (**9**), the respective 3,5-dialdehyde (**10**), and 3,5-bis(aminomethyl)-1-phenylpyrazole (**13**).

INTRODUCTION

Furfural (**1**), produced on technical scale from wood- and straw-derived xylans,[2] and its 5-hydroxymethyl derivative "HMF" (**2**), similarly accessible from renewable carbohydrate sources,[3-5] are key chemical intermediates, as they provide the starting materials for the production of various industrially important furans. In view of the vast perspectives in the use of low molecular weight carbohydrates as organic raw materials,[6] the acquisition of N-heterocycles from carbohydrates would be of similar importance, yet despite of the fact that the transformation of sugars into N-heterocycles occurs extensively on exposure of foodstuffs to heat (Maillard reaction),[7] and that various nitrogen heterocycles have been generated from saccharide derivatives,[8,9] practical procedures with conceivable large-scale adaptability are at present not available. Accordingly, the preparation of pyrrole by heating a glycerol solution of the ammonium salt of galactaric acid over a free flame[10] appears to be the highest-yielding conversion (40%) of this sort in the literature.
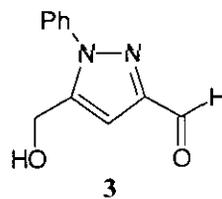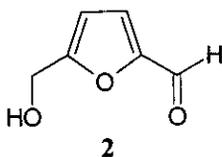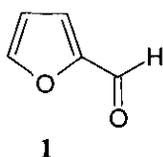
In studies directed towards the exploitation of the synthetic potential inherent in sugar-derived, hence hydrophilically substituted pyrroles, pyrazoles, pyridines, and pyridazines,[11] we have set out to either develop new methodologies for their acquisition from cheap, ton-scale available mono- and disaccharides, or to substantially improve existing procedures. We here report on an expeditious 4-step conversion of D-xylose into the 5-hydroxymethyl-1-phenylpyrazole-3-carboxaldehyde (3), a versatile intermediate for preparing – in one more step each – pyrazole building blocks with broad application profiles such as the 3,5-dicarboxylic acid (9), the respective dialdehyde (10), or the 3,5-bis(aminomethyl)derivative (13).

RESULTS AND DISCUSSION

Phenylosazones derived of various monosaccharides, amongst them D-xylose-derived 4, have been shown to elaborate a pyrazole ring upon refluxing in acetic anhydride,[12] involving a complex reaction sequence that conceivably proceeds in three consecutive steps: acetylation of the OH and NH groups,[12b] displacement of the 4-acetoxy function by the 2-phenylhydrazono nitrogen, and elimination of acetic acid from the pyrazoline thus formed; the yields obtained were modest, thus the resulting products were not exploited any further. In improving the conversion of D-xylose phenylosazone (4) into the phenylhydrazono-blocked pyrazolealdehyde (5),[12a] it was found advantageous to add the osazone to refluxing acetic anhydride, thereby effecting quick dissolution and, hence, short reaction times (1 h); in addition, by simply pouring the resulting reaction mixture onto ice, the crude pyrazolealdehyde phenylhydrazone (5) crystallized (91%); before being used for the ensuing reactions it is better recrystallized from aqueous ethanol, yielding pure 5 (79%). Various attempts to further improve upon the conversion of 4 → 5, e.g. by addition of zinc chloride or sodium acetate, gave inferior results.

The utility of 5 as a potential key compound for the generation of versatile building blocks rests on the efficiency with which deacetylation and/or liberation of the aldehyde function can be effected. Exposure of 5 to methanolic ammonia[12a] or to sodium methoxide/methanol readily and quantitatively removed the O-acetyl group (5 → 6), whilst de-N-acetylation required more forcing basic conditions, e.g. 0.5 N methanolic KOH, to yield the phenylhydrazone of pyrazolealdehyde (7) (70%). Liberation of the aldehyde function in 5 from its N-acetylphenylhydrazono protection was thought to be achievable by refluxing with benzaldehyde in aqueous acetic acid – conditions that have proved successful for the conversion of hexose phenylosazones into their osones.[13] This procedure though proved to be ineffective when applied to 5 or 6, obviously due to the N-acetyl group present, since the non-acetylated pyrazolephenylhydrazone (7) smoothly yielded to these conditions to afford the desired

5-hydroxymethyl-1-phenylpyrazole-3-carboxaldehyde (**3**) (60%). The direct removal of the
N-acetylphenylhydrazone residue from **5**, however, could be accomplished by using a more reactive
aldehyde: refluxing **5** with 35% aqueous formaldehyde/acetic acid provided an 89% yield of the acetyl
derivative (**8**), which on exposure to K_2CO_3 in aqueous methanol, was quantitatively converted into **3**.
Thus, a preparatively simple route is established from D-xylose, the most abundant and cheap pentose
available from renewable resources, to a versatile *N*-heterocyclic building block requiring four steps with
an overall yield of 57%.
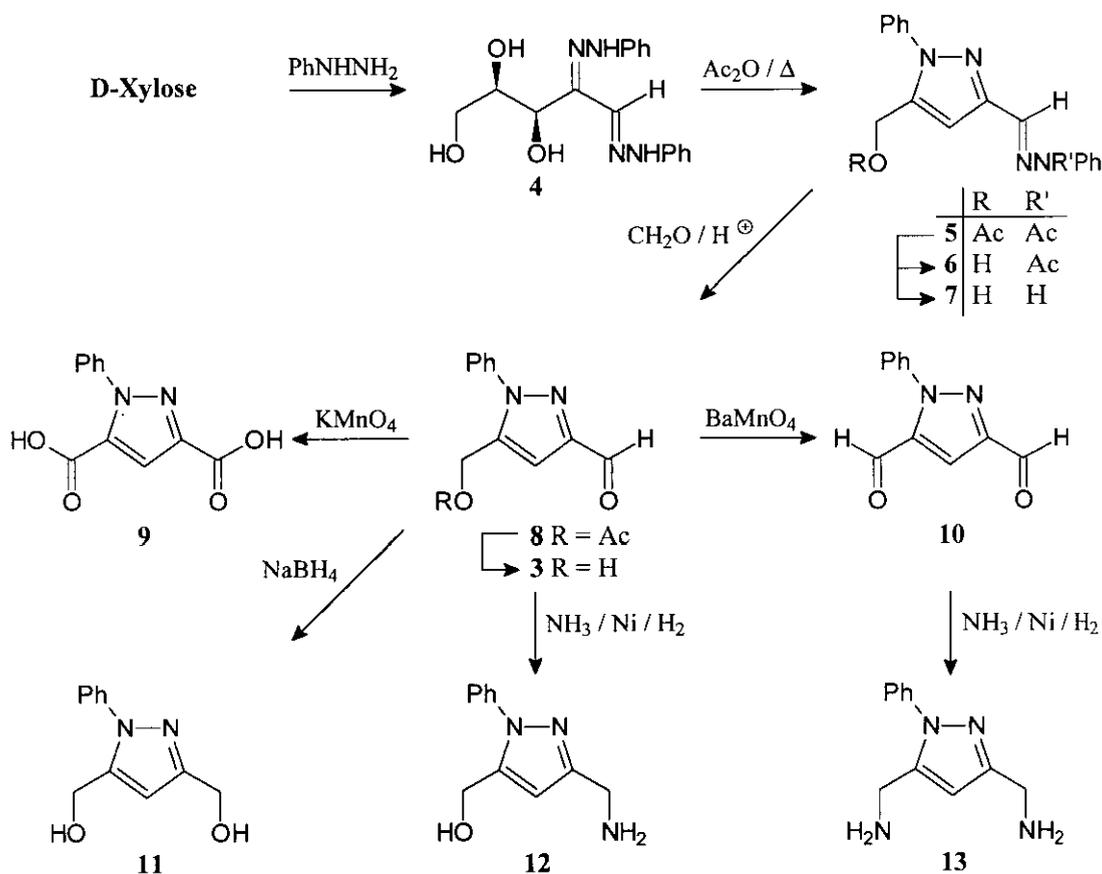
Further modification of pyrazolealdehyde (**3**) towards products with versatile application profiles
followed standard methodology: oxidation with potassium permanganate, or, alternately, with Pt/O_2 gave
the 3,5-dicarboxylic acid (**9**), exposure to $BaMnO_4$ in trichloroethane[14] afforded the respective dialdehyde
(**10**) (89%), whilst hydride reduction provided the bis(hydroxymethyl)pyrazole (**11**) (91%). Applying
reductive amination conditions, i.e. Raney nickel/ammonia[15] to either **3** or its dialdehyde (**10**), smoothly
elaborated the aminomethylpyrazole (**12**) and its bis(aminomethyl) analog (**13**), isolable in preparatively
useful yields of 85 and 79%, respectively.

Given the ready accessibility from a cheap and bulk scale accessible carbohydrate (57% for the four steps from D-xylose), pyrazolealdehyde (**3**) and the highly versatile heterocyclic building blocks (**9** - **13**) derived from it, can now be utilized towards the generation of novel polyamides by condensation of **9** with suitable diamines (**13** included) as well as of **13** with appropriate dicarboxylic acids such as adipic acid or **9**. Similarly, esterification of **9** with long-chain alcohols, or *N*-acylation of **13** with fatty acid chlorides are apt to lead to products with novel surfactant and/or liquid crystalline properties.

EXPERIMENTAL

Melting points (uncorrected values): Bock monoskop instrument. Spectral measurements: Perkin-Elmer 241 (rotations), Varian MAT 311 A (MS), and Bruker WM 300 instruments (^{1}H at 300, ^{13}C NMR at 75.5 MHz, respectively). TLC on Kieselgel 60 F_{254} plastic sheets (Merck) was used to monitor the reactions and to ascertain the purity of the products; eluants employed: 4:1 CH_3CN-H_2O, 3:1 toluene-EtOAc, 10:1 EtOH-2.5% aqueous NH_3; detection with UV-light or by charring with sulfuric acid. Column chromatography: Kieselgel 60 (63-200 mesh, Macherey-Nagel).

D-*threo*-Pentose phenylosazone (4). To a solution of D-xylose (15.0 g, 0.1 mol) in 150 mL of water was added phenylhydrazine (35 mL, 0.35 mol) and HOAc (5 mL), and the mixture was stirred for 2.5 h at 100°C. After addition of 100 mL of water to the still hot solution, the mixture was allowed to cool to rt and the crude osazone was filtered, washed with water and *n*-hexane, and recrystallized from aqueous MeOH: 26.6 g (81%) of **4** as yellow needles; mp 165 °C (lit.,[16] mp 164-165 °C, no yield given). ^{1}H NMR (DMSO-d_6): δ 3.37, 3.52 (2 m, 1 H each, 2 H-5), 3.62 (m, 1 H, H-4), 4.28 (t, J = 4.5 Hz, 1 H, H-3), 4.56 (t, J = 5.5 Hz, 1 H, 5-OH), 4.71 (d, J = 5.5 Hz, 1 H, 4-OH), 5.19 (d, J = 4.5 Hz, 1 H, 3-OH), 6.9-7.4 (m, 10 H, 2 C_6H_5), 7.86 (s, 1 H, 1-H), 10.73, 12.21 (2 s, 1 H each, 2 NH). ^{13}C NMR (DMSO-d_6): δ 63.1 (C-5), 73.8 (C-3), 75.0 (C-4), 134.7 (C-1), 137.7 (C-2). MS (FD): *m/z* 328 (M$^+$).

5-Acetoxymethyl-1-phenylpyrazole-3-carboxaldehyde *N*-acetylphenylhydrazone (**5**). Osazone (**4**) (18.0 g, 55 mmol) was added in portions to 100 mL of boiling acetic anhydride within the course of 10 min and the mixture was refluxed for another 50 min, followed by cooling to ambient temperature and pouring onto ice (150 mL) with vigorous stirring. After being kept in a refrigerator overnight, the precipitate was filtered off and washed with cold water to give 19.0 g (91%) of crude pyrazole (**5**) as brownish crystals of mp 178-180 °C. Purification by decolorizing a CH_2Cl_2 solution (200 mL) with neutral Al_2O_3 (1 g), filtration through celite, removal of the solvent from the filtrate, and recrystallization of the residue from aqueous EtOH afforded 16.5 g (79%) of **5** as colorless needles; mp 195-196 °C,

(lit.,[12a] mp 196 °C from EtOH). ^{1}H NMR (CDCl$_3$): δ 2.09 (s, 3 H, OCOCH_3), 2.61 (s, 3 H, NCOCH_3), 5.10 (s, 2 H, 5-CH_2), 6.96 (s, 1 H, H-4), 7.38 (s, 1 H, 3-CH), 7.1-7.5 (m, 10 H, 2 C$_6H_5$). ^{13}C NMR (CDCl$_3$): δ 20.9 (OCOCH_3), 22.2 (NCOCH_3), 56.3 (5-CH_2), 106.5 (C-4), 135.9 (3-CH), 138.9, 139.1 (C-3, C-5), 170.3 (OCOCH$_3$), 172.8 (NCOCH$_3$). MS (FD): m/z 376 (M$^+$).

5-Hydroxymethyl-1-phenylpyrazole-3-carboxaldehyde *N*-acetylphenylhydrazone (6). To a solution of 2.00 g (5.3 mmol) of **5** in dry MeOH (100 mL) was added NaOMe (75 mg), and the mixture was kept for 2 h at rt. Subsequently, the solution was neutralized with a strongly acidic ion exchange resin (Amberlite IR-120, H$^+$ form), filtered and the filtrate was taken to dryness *in vacuo*. Purification by elution from a silica gel column (3 x 30 cm) with 1:1 toluene-EtOAc and concentration of the eluates furnished 1.72 g (96%) of syrupy **6**, which crystallized after cooling; mp 155 °C (lit.,[12a] mp 155 °C). ^{1}H NMR (CDCl$_3$): δ 2.62 (s, 3 H, COCH_3), 2.84 (br s, 1 H, OH), 4.59 (d, J = 5.8 Hz, 2 H, 5-CH_2), 6.87 (s, 1 H, H-4), 7.1-7.5 (m, 11 H, 3-CH, 2 C$_6H_5$). ^{13}C NMR (CDCl$_3$): δ 22.3 (COCH_3), 55.6 (5-CH_2), 104.9 (C-4), 136.5 (3-CH), 139.2, 144.1 (C-3, C-5), 172.6 (COCH$_3$). MS (FD): m/z 334 (M$^+$). *Anal.* Calcd for C$_{19}$H$_{18}$N$_4$O$_2$: C, 68.25; H, 5.43; N, 16.76. Found C, 68.23; H, 5.55; N, 16.62.

5-Hydroxymethyl-1-phenylpyrazole-3-carboxaldehyde phenylhydrazone (7). Potassium hydroxide (1.5 g, 27 mmol) was added to a suspension of pyrazole (**5**) (1.0 g, 2.7 mmol) in dry MeOH (80 mL) and the mixture was stirred for 3 h at ambient temperature. Neutralization with a strongly acidic ion exchange resin (Amberlite IR-120, H$^+$ form), filtration of the mixture and removal of the solvent from the filtrate under reduced pressure yielded a residue, which was crystallized twice from aqueous EtOH: 555 mg (70%) of **7** as yellow needles; mp 160-161 °C. ^{1}H NMR (DMSO-d$_6$): δ 4.54 (d, J = 5.4 Hz, 2 H, 5-CH_2), 5.56 (t, J = 5.4 Hz, 1 H, OH), 6.80 (s, 1 H, H-4), 6.8-7.7 (m, 10 H, 2 C$_6H_5$), 7.92 (s, 1 H, 3-CH) 10.38 (s, 1 H, NH). ^{13}C NMR (DMSO-d$_6$): δ 54.3 (5-CH_2), 104.1 (C-4), 130.7 (3-CH), 139.3, 144.5 (C-3, C-5). MS (FD): m/z 292 (M$^+$). *Anal.* Calcd for C$_{17}$H$_{16}$N$_4$O: C, 69.84; H, 5.52; N, 19.17. Found: C, 69.65; H, 5.43; N, 19.22.

5-Acetoxymethyl-1-phenylpyrazole-3-carboxaldehyde (8). To a suspension of pyrazole (**5**) (10.0 g, 27 mmol) in 100 mL of EtOH and 120 mL (1.4 mol) of a 35% aqueous formaldehyde solution was added 5 mL of HOAc, and the mixture was heated to 100 °C for 7 h. Subsequently, the solution was concentrated under reduced pressure, neutralized (satd. NaHCO$_3$ solution), and extracted with EtOAc (4 x 100 mL). The combined organic phases were washed with water (2 x 50 mL), and dried (MgSO$_4$). Evaporation of the solvent gave a residue which was purified by elution from a silica gel column (4.5 x 30 cm) with 3:1 toluene-EtOAc. Removal of the solvents from the appropriate eluates with R_f 0.31 afforded **8** (5.8 g, 89%) as a yellowish syrup. ^{1}H NMR (CDCl$_3$): δ 1.97 (s, 3 H, COCH_3), 5.02 (s, 2 H,

5-CH_2), 6.92 (s, 1 H, H-4), 7.1-7.5 (m, 5 H, C$_6$H$_5$), 9.92 (s, 1 H, CHO). ^{13}C NMR (CDCl$_3$): δ 20.7 (COCH_3), 56.5 (5-CH_2), 108.2 (C-4), 138.6, 140.1 (C-3, C-5), 170.1 (COCH$_3$), 186.6 (CHO). MS (FD): m/z 244 (M$^+$). *Anal.* Calcd for C$_{13}$H$_{12}$N$_2$O$_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.97; H, 4.80; N, 11.52.

The eluates with R_f 0.18 (3:1 toluene-EtOAc) gave upon evaporation of the solvents *in vacuo* 300 mg of amorphous **formaldehyde N-acetylphenylhydrazone**. ^{1}H NMR (CDCl$_3$): δ 2.49 (s, 3 H, COCH_3), 6.20, 6.38 (2 d, J = 10.8 Hz, 1 H each, CH_2), 7.1-7.5 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (CDCl$_3$): δ 22.1 (COCH$_3$), 129.3, 129.5, 130.3, 135.1 (C$_6$H$_5$), 131.7 (CH$_2$), 172.8 (COCH$_3$). MS (FD): m/z 162 (M$^+$).

5-Hydroxymethyl-1-phenylpyrazole-3-carboxaldehyde (3).

a) *By de-O-acetylation of acetoxymethylpyrazolecarboxaldehyde* (**8**): To a solution of **8** (5.1 g, 21 mmol) in MeOH and water (100 mL each) was added K$_2$CO$_3$ (2.9 g, 21 mmol) and the mixture was stirred for 30 min at ambient temperature. After removal of MeOH under reduced pressure, 100 mL of water was added, followed by extraction with CH$_2$Cl$_2$ (3 x 100 mL), drying of the organic phases (MgSO$_4$), and concentration to a syrup which was crystallized from *i*PrOH. Collection by filtration gave 4.2 g (quant.) of **3**; mp 87-88 °C. ^{1}H NMR (CDCl$_3$): δ 3.01 (t, J = 5.4 Hz, 1 H, OH), 4.64 (d, J = 5.4 Hz, 2 H, 5-CH_2), 6.92 (s, 1 H, H-4), 7.5-7.6 (m, 5 H, C$_6$H$_5$), 9.98 (s, 1 H, CHO). ^{13}C NMR (CDCl$_3$): δ 55.5 (5-CH_2), 107.0 (C-4), 138.9, 144.8 (C-3, C-5), 187.1 (CHO). MS (FD): m/z 202 (M$^+$). *Anal.* Calcd for C$_{11}$H$_{10}$N$_2$O$_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.04; H, 5.06; N, 13.77.

b) *From 7 by transfer of the phenylhydrazine residue to benzaldehyde:* In adaption of the Bayne variant for converting glucose phenylosazone into glucosone,[13] a suspension of phenylhydrazone (**7**) (585 mg, 2.0 mmol) in 50 mL of 2:1 water-ethanol was refluxed with benzaldehyde (0.6 mL, 6 mmol) for 4 h, followed by workup as described above under a), to give **3** (240 mg, 60%); mp 87-88 °C.

1-Phenylpyrazole-3,5-dicarboxylic acid (9).

To a suspension of pyrazole (**3**) (405 mg, 2.0 mmol) in 30 mL of water was added 640 mg (4.1 mmol) of KMnO$_4$ and the mixture was heated to reflux for 2 h. The mixture was filtered through celite, unpolar byproducts were removed by extraction with ether (3 x 30 mL), and the aqueous phase was made slightly acidic by the addition of 2N HCl. After cooling to 0 °C for several days, the dicarboxylic acid (**9**) (360 mg, 75%) was isolated as colorless needles; mp 270 °C, (lit.,[12a,17] mp 270 °C for a sample prepared from hexoses; no yield given). ^{1}H NMR (DMSO-d$_6$): δ 7.36 (s, 1 H, H-4), 7.5-7.6 (m, 5 H, C$_6$H$_5$), 13.5 (br s, 2 H, 2 CO$_2$H). ^{13}C NMR (DMSO-d$_6$): δ 113.8 (C-4), 135.6, 139.8 (C-3, C-5), 159.3, 162.3 (2 CO$_2$H). MS (FD): m/z 232 (M$^+$). *Anal.* Calcd for C$_{11}$H$_8$N$_2$O$_4$: C, 56.90; H, 3.47; N, 12.06. Found: C, 57.2; H, 3.52; N, 12.03.

1-Phenylpyrazole-3,5-dicarboxaldehyde (10). BaMnO$_4$ (5.9 g, 23 mmol) was added to a solution of 920 mg (4.5 mmol) of pyrazole (**3**) in 100 mL of 1,1,2-trichloroethane and the mixture was refluxed for 3 h. The mixture was filtered through celite, washed thoroughly with CH$_2$Cl$_2$, and concentrated under reduced pressure to left a residue, which was purified by elution from silica gel (3 x 30 cm) with 9:1 toluene-EtOAc. Evaporation of the eluate to dryness afforded 790 mg (89%) of syrupy **10**, which gradually crystallized; mp 84-85 °C. ^{1}H NMR (CDCl$_3$): δ 7.5-7.6 (m, 6 H, H-4, C$_6$H$_5$), 9.89, 10.09 (2 s, 1 H each, 2 C*HO*). ^{13}C NMR (CDCl$_3$): δ 111.6 (C-4), 138.3, 141.6 (C-3, C-5), 179.6, 185.8 (2 CHO). MS (FD): *m/z* 200 (M$^+$). *Anal.* Calcd for C$_{11}$H$_8$N$_2$O$_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 66.00; H, 3.86; N, 13.91.

3,5-Bis(hydroxymethyl)-1-phenylpyrazole (11). To a stirred solution of **3** (893 mg, 4.4 mmol) in *i*PrOH (100 mL) was added NaBH$_4$ (170 mg, 4.5 mmol), and stirring was continued for 2 h at ambient temperature. Decomposition of excessive NaBH$_4$ by the addition of few drops of HOAc and removal of the solvent *in vacuo* left a syrup which was purified by elution from a silica gel column (2.5 x 27 cm) with EtOAc. Concentration of the appropriate eluates gave 817 mg (91%) of **11** as an uniform syrup. ^{1}H NMR (CDCl$_3$): δ 4.49 (m, 4 H, 3-C*H$_2$*, 5-C*H$_2$*), 5.15, 5.49 (2 t, *J* = 5.7 and 5.4 Hz, 1 H each, 2 OH), 6.43 (s, 1 H, H-4), 7.4-7.7 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (CDCl$_3$): δ 54.2 (5-*CH$_2$*), 57.2 (3-*CH$_2$*), 106.4 (*C*-4), 139.5, 143.7 (C-3, C-5). MS (FD): *m/z* 204 (M$^+$). *Anal.* Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.38; H, 5.99; N, 13.67.

3-Aminomethyl-5-hydroxymethyl-1-phenylpyrazole (12). In a hydrogenation vessel a solution of 978 mg (4.8 mmol) of **3** in 50 mL of methanolic NH$_3$ (5 M) was stirred for 30 min at rt, followed by the addition of Raney nickel (700 mg) and vigourous shaking in a hydrogen atmosphere for 14 h. The catalyst was filtered off, washed with MeOH, and the filtrate was concentrated *in vacuo* to a syrup which was purified by elution from a silica gel column (3.5 x 32 cm) with 10:1 EtOH/2.5% aqueous NH$_3$. Removal of the solvents from the eluates furnished an uniform syrup, which crystallized after cooling to yield 833 mg (85%) of **12** of mp 84-85 °C. ^{1}H NMR (CDCl$_3$): δ 2.91 (br s, 3 H, NH$_2$, OH), 3.79 (s, 2 H, 3-C*H$_2$*), 4.46 (s, 2 H, 5-C*H$_2$*), 6.21 (s, 1H, H-4), 7.3-7.5 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (CDCl$_3$): δ 39.7 (3-CH$_2$), 55.0 (5-CH$_2$), 105.6 (C-4), 139.6, 144.0 (C-3, C-5). MS (FD): *m/z* 204 (M$^+$+1). *Anal.* Calcd for C$_{11}$H$_{13}$N$_3$O: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.78; H, 6.34; N, 20.46.

3,5-Bis(aminomethyl)-1-phenylpyrazole dihydrochloride (13·2 HCl). In a hydrogenation vessel, Raney nickel (500 mg) was added to a solution of 387 mg (1.9 mmol) of dialdehyde (**10**) in 30 mL of methanol saturated with NH$_3$ (5 M) and the mixture was stirred for 14 h in a hydrogen atmosphere. The catalyst was filtered off and washed thoroughly with MeOH. Freed from the solvent *in vacuo* gave a

residue which was purified by elution from a silica gel column (2 x 23 cm) with 10:1 EtOH-2.5% aqueous NH$_3$. Concentration of the fractions containing **13** gave a residue which was dissolved in 2 N HCl for characterization. Evaporation *in vacuo* yielded 413 mg (79%) of the bis(hydrochloride) of **13** as an amorphous powder. ^{1}H NMR (DMSO-d$_6$): δ 4.07 (m, 4 H, 3-C*H*$_2$, 5-C*H*$_2$), 6.94 (s, 1 H, H-4), 7.5-7.6 (m, 5 H, C$_6$*H*$_5$), 8.65, 8.97 (2 br s, 3 H each, 2 NH$_3^+$). ^{13}C NMR (DMSO-d$_6$): δ 34.2, 36.4 (3-CH$_2$, 5-CH$_2$), 107.5 (C-4), 138.2, 138.6 (C-3, C-5). MS (FD): *m/z* 204 (M^{2+}). *Anal.* Calcd for C$_{11}$H$_{14}$N$_4$·2 HCl: C, 48.01; H, 5.86; N, 20.36. Found: C, 48.25; H, 5.81; N, 20.2.

ACKNOWLEDGEMENTS

REFERENCES AND NOTES

1. This account is Part 21 of a series on "Building Blocks from Sugars". Part 20: ref. 6.

2. W. J. McKillip, in 'Ullmann's Encyclop. Industrial Chem.', 5th Ed., VCH Publ., Weinheim/New York, 1989, **A12**, pp. 122-125.

3. B. F. M. Kuster, *Starch/Stärke*, 1990, **42**, 314.

4. H. Schiweck, M. Munir, K. M. Rapp, B. Schneider, and M. Vogel, in 'Carbohydrates as Organic Raw Materials', ed. by F.W. Lichtenthaler, VCH Publ., Weinheim/New York, 1991, pp. 78-82.

5. L. Cottier and G. Descotes, *Trends Heterocycl. Chem.*, 1991, **2**, 233.

6. F. W. Lichtenthaler and S. Mondel, *Pure Appl. Chem.*, 1997, **69**, 1853.

7. G. P. Ellis, *Adv. Carbohydr. Chem.*, 1959, **14**, 63. – F. Ledl and E. Schleicher, *Angew. Chem.*, 1990, **102**, 597; *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 565.

8. M. J. Kort, *Adv. Carbohydr. Chem. Biochem.*, 1970, **25**, 311.

9. H. El Khadem, *Adv. Carbohydr. Chem. Biochem.*, 1970, **25**, 351.

10. H. Schwanert, *Ann. Chem.*, 1860, **116**, 278. – S. M. McElvain and K. M. Bolliger, *Org. Synth., Coll. Vol., 1*, 1941, 473.

11. A first report on these studies was presented: E. Cuny, 9th European Carbohydrate Symposium, Utrecht, July 1997, Abstract E1.

12. a) H. El Khadem and M. M. Mohammed-Aly, *J. Chem. Soc.*, 1963, 4929. – b) H. El Khadem, Z. El Shafei, and M. A. Abdel Rahman, *Carbohydr. Res.*, 1965, **1**, 31. – c) H. S. El Khadem, Z. El Shafei, E. S. El Ashry, and M. El Sadek, *Carbohydr. Res.*, 1976, **49**, 185. – d) L. Somogyi, *Carbohydr. Res.*, 1985, **144**, 71.

13. E. Fischer and E. F. Armstrong, *Ber.*, 1902, **35**, 3141. – S. Bayne, *Methods Carbohydr. Chem.*, 1963, **2**, 421.

14. This procedure has proved successful to convert HMF (**2**) into furan-2,5-dicarboxaldehyde: H. Firouzabadi and E. Ghaderi, *Tetrahedron Lett.*, 1978, 839. – T. El Hajj, A. Masroua, J.-C. Martin, and G. Descotes, *Bull. Soc. Chim. Fr.*, 1987, **5**, 855.

15. A. Fürst, R. C. Berlo, and S. Hooton, *Chem. Rev.*, 1965, **65**, 51.

16. N. K. Richtmyer, *Methods Carbohydr. Chem.*, 1963, **2**, 129.

17. L. Claisen and P. Roosen, *Ann. Chem.*, 1894, **278**, 274.