# Synthesis of *N*¹-Aryl- and *N*¹-Benzyl Substituted Imidazole-4- and Imidazole-5-carbaldehydes

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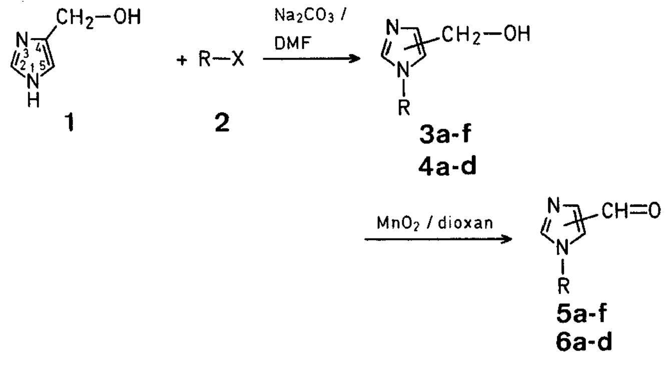
In order to synthesize several $N^1$-aryl- and $N^1$-benzylimidazole-4-carbaldehydes as intermediates of potential antitumor agents[1], we have developed a convenient route starting from 4(5)-hydroxymethylimidazole (**1**) which requires only two steps. The starting material **1** was obtained in an overall yield of 60% from fructose by a known method[2]. Treatment of the alcohol **1** with aryl or benzyl halides **2** in dimethylformamide containing sodium carbonate at 100 °C for 7–18 h yielded a mixture of $N^1$-aryl or -benzyl-4-hydroxymethylimidazole (**3**) and $N^1$-aryl or -benzyl-5-hydroxymethylimidazole (**4**) in a variable ratio. The structures of the isomer pairs **3** and **4** were determined on the basis of their $^1$H-N.M.R. spectra (Table 1).



It has been reported[3] that 1,4- and 1,5-disubstituted imidazole isomers have different values of the cross-ring coupling constants in dimethyl sulfoxide. In particular $J_{2,5}$ is larger than $J_{2,4}$ (1.1–1.5 Hz vs. 0.9–1.0 Hz). We were able to determine these values for the isomer pairs **3, 4a** and **3, 4d** (Table 1) and, on this basis, the structure assignment was made. The $^1$H-N.M.R. spectra indicates that for each isomer pair, the benzylic methylene protons of the 4-isomer are more deshielded compared with those of the 5-isomer. Based on this, we assigned the structure of the isomer pairs **3, 4b** and **3, 4c** for which it was impossible to determine the imidazolic proton coupling constants.

The arylation of compound **1** with *o*-nitrophenyl fluoride or *p*-nitrophenyl fluoride generated only one isomer. For these compounds it was impossible to make the structure assignment based on $^1$H-N.M.R. spectra because we were inable to measure the $J_{2,4}$ or $J_{2,5}$ values and could not compare the isomer pairs' chemical shifts. The structures were determined indirectly after oxidation to the corresponding aldehydes **5e** and **5f** for which we measured the $J_{2,5}$ values as 1.20 and 1.25 Hz, respectively. The structure assignment is supported by thermodynamic considerations. In fact $S_NAr$ reactions are almost exclusively bimolecular and therefore more susceptible to steric effects; so in our case formation of 1,5-isomer is sterically hindered and the 1,4-isomer should predominate. Also the other alcohols **3a–d** and **4a–d** were then oxidized with activated manganese(IV) oxide in dioxan to the corresponding aldehydes **5a–d** and **6a–d** in good yields.

**4(5)-Hydroxymethylimidazole (1):**

Prepared according to Ref.[2] and worked up as follows: The solution obtained by filtration of the copper sulfide is evaporated to dryness and the residue is chromatographed on a silica gel column eluting with ethyl acetate/methanol/36% ammonia (65/30/5); yield: 54 g (60%) from 90 g of fructose.

**$N^1$-Benzyl-4-hydroxymethylimidazole (3a) and $N^1$-Benzyl-5-hydroxymethylimidazole (4a):**

A suspension of 4(5)-hydroxymethylimidazole (**1**; 3 g, 31 mmol), anhydrous sodium carbonate (3.3 g, 31 mmol), and benzyl bromide (7.0 g, 32 mmol) in dimethylformamide (50 ml) is heated at 100 °C with stirring (Table 1). After cooling, the mixture is diluted with water (50 ml), filtered, and extracted several times with chloroform (30–40 ml each time). The dried (sodium sulfate) chloroform solution is evaporated to leave a residue which is chromatographed on a silica gel column (ethyl acetate/methanol/36% ammonia; 89/10/1) to give **4a** (yield: 0.42 g) and **3a** (yield: 1.27 g).

**$N^1$-(2-Nitrobenzyl)-4-hydroxymethylimidazole (3b) and $N^1$-(2-Nitrobenzyl)-5-hydroxymethylimidazole (4b):**

The reaction is carried out with the alcohol **1** and 2-nitrobenzyl chloride and worked up as described above. Evaporation of the chloroform solution affords an oil which is induced to crystallize by cooling. The solid is filtered and recrystallized from 2-methoxyethanol to give **3b** as pale yellow crystals. The filtrate is chromatographed on a silica

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Table 1. $N^1$-Substituted 4- and 5-Hydroxymethylimidazoles **3a-f** and **4a-d**

| Product No. | R | X | Reaction time [h] | Yield [%] | m.p. [°C] (solvent) | Molecular Formula[a] | $^1$H-N.M.R. (DMSO-$d_6$)[b] δ [ppm] (CH$_2$O; CH$_2$N; 4- or 5-H; 2-H) | $J_{2,4}$ or $J_{2,5}$[c] [Hz] |
|---|---|---|---|---|---|---|---|---|
| **3a** | $C_6H_5CH_2$ | Br | 13 | 22 | 82-83° ($CH_3COOC_2H_5$) | $C_{11}H_{12}N_2O$ (188.2) | 4.38 (s); 5.17 (s); 7.05 (s); 7.72 (s) | 1.20 |
| **4a** | $C_6H_5CH_2$ | Br | 13 | 7 | 134-135° ($CH_3COOC_2H_5$) | $C_{11}H_{12}N_2O$ (188.2) | 4.37 (s); 5.28 (s); 6.89 (s); 7.71 (s) | 0.90 |
| **3b** | $2\text{-}O_2N{-}C_6H_4CH_2$ | Cl | 7 | 65 | 138-139° ($CH_3OCH_2CH_2OH$) | $C_{11}H_{11}N_3O_3$ (233.2) | 4.37 (s); 5.56 (s); 7.04 (s); 7.69 (s) | – |
| **4b** | $2\text{-}O_2N{-}C_6H_4CH_2$ | Cl | 7 | 30 | 155-156° ($CH_3OCH_2CH_2OH$) | $C_{11}H_{11}N_3O_3$ (233.2) | 4.30 (s); 5.66 (s); 6.93 (s); – | – |
| **3c** | $3\text{-}O_2N{-}C_6H_4CH_2$ | Cl | 12 | 45 | 160-162° ($CH_3OCH_2CH_2OH$) | $C_{11}H_{11}N_3O_3$ (233.2) | 4.37 (d); 5.33 (s); 7.12 (s); – | – |
| **4c** | $3\text{-}O_2N{-}C_6H_4CH_2$ | Cl | 12 | 20 | 172-174° ($CH_3OCH_2CH_2OH$) | $C_{11}H_{11}N_3O_3$ (233.2) | 4.37 (d); 5.42 (s); 6.89 (s); 7.78 (s) | – |
| **3d** | $4\text{-}O_2N{-}C_6H_4CH_2$ | Br | 18 | 50 | 175-177° ($CH_3OCH_2CH_2OH$) | $C_{11}H_{11}N_3O_3$ (233.2) | 4.38 (s); 5.35 (s); 7.07 (s); 7.73 (s) | 1.20 |
| **4d** | $4\text{-}O_2N{-}C_6H_4CH_2$ | Br | 18 | 30 | 201-203° ($CH_3OCH_2CH_2OH$) | $C_{11}H_{11}N_3O_3$ (233.2) | 4.40 (s); 5.50 (s); 6.97 (s); 7.86 (s) | 0.96 |
| **3e** | $2\text{-}O_2N{-}C_6H_4$ | F | 18 | 98 | 153-155° ($C_2H_5OH$) | $C_{10}H_9N_3O_3$ (219.2) | 4.48 (d); –; 7.27 (s); – | – |
| **3f** | $4\text{-}O_2N{-}C_6H_4$ | F | 18 | 85 | 172-173° ($C_2H_5OH$) | $C_{10}H_9N_3O_3$ (219.2) | 4.45 (d); –; 7.97 (s); 8.40 (s) | – |

[a] Satisfactory microanalyses were obtained (C ±0.34, H ±0.30, N ±0.29).

[b] $^1$H-N.M.R. spectra were recorded at 90 MHz on a Varian EM-390 spectrometer using TMS as internal standard.

[c] Measured at 100 °C.

Table 2. $N^1$-Substituted Imidazole-4- and -5-carboxaldehydes **5a-f** and **6a-d**

| Product No. | R | Reaction time [h] | Yield [%] | m.p. [°C] | Molecular Formula[a] | | I.R. (Nujol)[b] $\nu_{C=O}$ [cm$^{-1}$] | $^1$H-N.M.R. (DMSO-$d_6$)[c] δ [ppm] CHO |
|---|---|---|---|---|---|---|---|---|
| **5a** | $C_6H_5CH_2$ | 12 | 65 | oil | $C_{11}H_{10}N_2O$ | (186.2) | 1670 | 9.79 |
| **6a** | $C_6H_5CH_2$ | 6 | 63 | oil | $C_{11}H_{10}N_2O$ | (186.2) | 1665 | 9.89 |
| **5b** | $2\text{-}O_2N{-}C_6H_4CH_2$ | 9 | 48 | 91-93° | $C_{11}H_9N_3O_3$ | (231.2) | 1675 | 9.80 |
| **6b** | $2\text{-}O_2N{-}C_6H_4CH_2$ | 17 | 24 | 114-116° | $C_{11}H_9N_3O_3$ | (231.2) | 1680 | 9.76 |
| **5c** | $3\text{-}O_2N{-}C_6H_4CH_2$ | 7 | 50 | 121-123° | $C_{11}H_9N_3O_3$ | (231.2) | 1680 | 9.85 |
| **6c** | $3\text{-}O_2N{-}C_6H_4CH_2$ | 18 | 14 | 102-103° | $C_{11}H_9N_3O_3$ | (231.2) | 1665 | 9.80 |
| **5d** | $4\text{-}O_2N{-}C_6H_4CH_2$ | 8 | 38 | 156-158° | $C_{11}H_9N_3O_3$ | (231.2) | 1670 | 9.80 |
| **6d** | $4\text{-}O_2N{-}C_6H_4CH_2$ | 8 | 10 | 123-125° | $C_{11}H_9N_3O_3$ | (231.2) | 1665 | 9.73 |
| **5e** | $2\text{-}O_2N{-}C_6H_4$ | 1.5 | 76 | 91-92° | $C_{10}H_7N_3O_3$ | (217.2) | 1695 | 9.88[d,e] |
| **5f** | $4\text{-}O_2N{-}C_6H_4$ | 1.5 | 87 | 204-205° | $C_{10}H_7N_3O_3$ | (217.2) | 1695 | 9.90[e,f] |

[a] Satisfactory microanalyses were obtained (C ±0.31, H ±0.30, N ±0.29).

[b] I.R. spectra were recorded on a Perkin Elmer 297 spectrometer.

[c] $^1$H-N.M.R. spectra were measured at 90 MHz with a Varian EM-390 spectrometer using TMS as internal standard.

[d] $J_{2,5}$ = 1.20 Hz.

[e] Measured at 80 °C on a Varian XL100 spectrometer.

[f] $J_{2,5}$ = 1.25 Hz.

gel column (ethyl acetate/methanol/36% ammonia; 80/19/1) to yield the isomer **4b** and a further amount of the isomer **3b**.

**$N^1$-(3-Nitrobenzyl)-4-hydroxymethylimidazole (3c) and $N^1$-(3-Nitrobenzyl)-5-hydroxymethylimidazole (4c):**

The reaction is carried out with the alcohol **1** and 3-nitrobenzyl chloride and worked up as described above. Evaporation of the chloroform solution leaves an oily residue which is induced to crystallize by addition of ethyl acetate/methanol. The solid is filtered and column chromatographed on silica gel (ethyl acetate/methanol/36% ammonia; 80/19/1) to give **4c** and then **3c**.

**$N^1$-(4-Nitrobenzyl)-4-hydroxymethylimidazole (3d) and $N^1$-(4-Nitrobenzyl)-5-hydroxymethylimidazole (4d):**

The reaction is carried out with the alcohol **1** and 4-nitrobenzylbromide and worked up as described for the compounds **3c** and **4c**.

**$N^1$-(2-Nitrophenyl)-4-hydroxymethylimidazole (3e) and $N^1$-(4-Nitrophenyl)-4-hydroxymethylimidazole (3f):**

The reaction is carried out with the alcohol **1** and 1-fluoro-2-nitrobenzene or 1-fluoro-4-nitrobenzene as described above. The reaction mixture is filtered. The filtrate is poured on ice to give a solid which is recrystallized from ethanol.

**$N^1$-Substituted Imidazole-4-carbaldehydes 5 and Imidazole-5-carbaldehydes 6; General Procedure:**

A stirred mixture of one of the alcohols **3a-f** or **4a-d** (4.2 mmol) and activated manganese(IV) oxide (3.6 g, 41 mmol) in dioxan (25 ml) is refluxed (Table 2). The manganese oxide is filtered and the filtrate evaporated to dryness in vacuo; the residue is chromatographed on a silica gel column eluting with ethyl acetate/methanol (9/1) (chloroform/methanol, 9/1 in the case of **5d** and **6d**) to give the respective aldehyde **5** or **6** (Table 2).

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