# Synthesis of Imidazo[1,2-*a*]pyridines from 1-(2-Alkynyl)-2-aminomethylimidazoles

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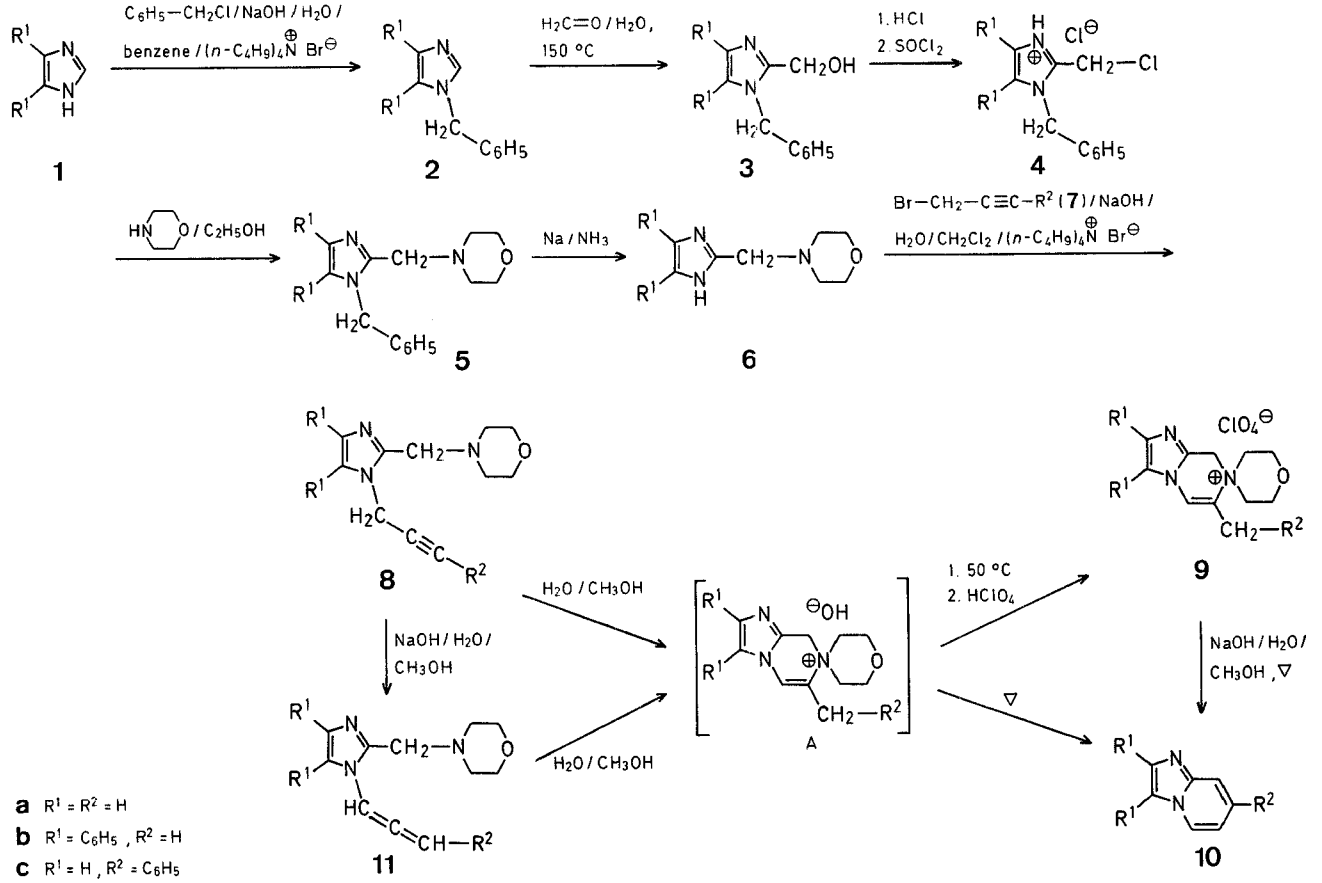
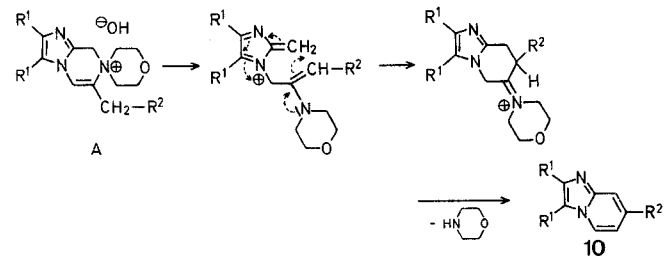
A series of imidazo[1,2-*a*]pyridines have been synthesized as potential anthelmintic or bacteriostatic drugs[1,2,3]. Except for some uncommon examples[4], these compounds are usually prepared by the reaction of 2-aminopyridine with bifunctional compounds such as α-chloroketones or 1-halo-2-alkynes[5,6,7]. We now report a new synthetic approach starting from imidazoles (**1**) using the following reaction sequence.




**a** $R^1 = R^2 = H$
**b** $R^1 = C_6H_5$, $R^2 = H$
**c** $R^1 = H$, $R^2 = C_6H_5$

The formation of compounds **9** and **10** is assumed to proceed via the spirocyclic ammonium hydroxide A as an intermediate[8,9]. This intermediate A, which can be formed from **8** or **11**, probably is converted into **10** via an enamine intermediate in the following manner:



The synthesis of compounds **10** described here which involves anellation of imidazoles instead of the usually employed anellation of 2-aminopyridine consists of a sequence of only simple procedures which can even be performed without purification of the intermediate products between the individual reaction steps. The sequence provides the possibility of preparing imidazo[1,2-*a*]pyridines (**10**) containing substituents such as aryl groups which cannot be introduced into imidazo[1,2-*a*]pyridines by electrophilic substitution.

Melting points are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 model. I.R. spectra were measured using a Perkin-Elmer 137 E spectrometer. $^1$H-N.M.R. spectra were recorded on Varian T 60 or EM 390 spectrometers.

Commercial imidazole is used. 4,5-Diphenylimidazole[12] (**1**, $R^1 = C_6H_5$), 1-benzylimidazole[13] (**2**, $R^1 = H$), 1-benzyl-4,5-diphenylimidazole[13] (**2**, $R^1 = C_6H_5$), and 3-bromo-1-phenyl-1-propyne[14] (**7**, $R^2 = C_6H_5$) are prepared by known methods.

**1-Benzyl-2-hydroxymethylimidazoles (3); General Procedure:**
A mixture of aqueous formaldehyde (d = 1.08; 25 ml) and the 1-benzylimidazole (**2**; 0.1 mol) is heated in a closed reactor at 150 °C for 3 h. After cooling, the mixture is treated with water (200 ml) and extracted with dichloromethane (3 × 30 ml). The organic layer is washed with water (2 × 50 ml), dried with sodium sulfate, and evaporated to give the crude product **3**.

*1-Benzyl-2-hydroxymethylimidazole* (**3**, $R^1 = H$) is obtained as an oil; yield: 92%. It is converted into the hydrochloride by treatment with gaseous hydrogen chloride in dichloromethane; m.p. of hydrochloride: 161–163 °C (from isopropanol) (Ref.[15], m.p. 161 °C).

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta = 4.60$ (s, 2H); 5.18 ppm (s, 2H).

*1-Benzyl-2-hydroxymethyl-4,5-diphenylimidazole* (**3**, $R^1 = C_6H_5$) is recrystallized from methanol; yield: 90%; m.p. 200–202 °C.

| | | | | |
|---|---|---|---|---|
| $C_{23}H_{20}N_2O$ | calc. | C 81.17 | H 5.88 | N 8.23 |
| (340.4) | found | 81.25 | 6.03 | 8.10 |

$^1$H-N.M.R. (DMSO-$d_6$/$TMS_{int}$): $\delta = 4.60$ (s, 2H); 5.21 ppm (s, 2H).

**1-Benzyl-2-morpholinomethylimidazoles (5); General Procedure:**
A mixture of the 1-benzyl-2-hydroxymethylimidazole (**3**) hydrochloride (0.1 mol) and thionyl chloride (24 g, 0.2 mol) is stirred at room temperature for 30 min. Unreacted thionyl chloride is then removed in vacuo to leave the crude *1-benzyl-2-chloromethylimidazole hydrochlo-*

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*ride* (**4**). To this is added, slowly and with stirring, ethanol (120 ml) and morpholine (35 ml, 0.4 mol). The reaction is exothermic. After the mixture has cooled to room temperature the precipitated morpholine hydrochloride is filtered off and the filtrate is evaporated in vacuo. The residual product **5** may be purified by recrystallization.

*1-Benzyl-2-morpholinomethylimidazole* (**5**, $R^1$ = H); yield: 83%; m.p. 170 °C (ethyl acetate).

| | | | | |
|---|---|---|---|---|
| $C_{15}H_{19}N_3O$ | calc. | C 70.03 | H 7.39 | N 16.34 |
| (257.3) | found | 69.91 | 7.54 | 16.23 |

$^1$*H*-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.3 (t, 4H); 3.50 (t, 4H); 3.50 ppm (s, 2H).

*1-Benzyl-2-morpholinomethyl-4,5-diphenylimidazole* (**5**, $R^1 = C_6H_5$); yield: 86%; m.p. 130 °C (isopropanol).

| | | | | |
|---|---|---|---|---|
| $C_{27}H_{27}N_3O$ | calc. | C 79.16 | H 6.59 | N 10.25 |
| (409.5) | found | 79.31 | 6.48 | 10.35 |

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.45 (t, 4H); 3.65 (t, 4H); 3.68 ppm (s, 2H).

**2-Morpholinomethylimidazoles (6); General Procedure[15,16]:**
To a stirred solution of the 1-benzyl-2-morpholinomethylimidazole (**5**; 0.1 mol) in liquid ammonia (300 ml), sodium (5.1 g, 0.22 mol) is added over 10 min. The mixture becomes dark blue. Stirring is continued for 3 min and ammonium chloride (27 g, 0.5 mol) is cautiously added. After complete evaporation of ammonia, the remaining solid is extracted with boiling dichloromethane (5 × 100 ml). Dichloromethane is eliminated in vacuo to leave product **6** which may be purified by recrystallization.

*2-Morpholinomethylimidazole* (**6**, $R^1$ = H); yield: 74%; m.p. 128–130 °C.

| | | | | |
|---|---|---|---|---|
| $C_8H_{13}N_3O$ | calc. | C 57.41 | H 7.77 | N 25.12 |
| (167.2) | found | 57.11 | 7.63 | 25.19 |

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.45 (t, 4H); 3.65 (t, 4H); 3.65 (s, 2H); 6.95 (s, 2H); 9.65 ppm (s, 1H).

*2-Morpholinomethyl-4,5-diphenylimidazole* (**6**, $R^1 = C_6H_5$); yield: 82%; m.p. 168–171 °C (methanol).

| | | | | |
|---|---|---|---|---|
| $C_{20}H_{21}N_3O$ | calc. | C 75.20 | H 6.58 | N 13.14 |
| (319.4) | found | 75.52 | 6.11 | 13.19 |

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.55 (t, 4H); 3.60 (s, 2H); 3.65 ppm (t, 4H).

**1-(2-Alkynyl)-2-morpholinomethylimidazoles (8); General Procedure:**
To a solution of the 2-morpholinomethylimidazole (**6**; 0.1 mol) in dichloromethane (60 ml) are added the 1-bromo-2-alkyne (**7**; 0.1 mol), aqueous sodium hydroxide (d = 1.38; 15 ml), and tetrabutylammonium bromide (0.5 g), and the mixture is stirred for 2 h at −5° to 0 °C. The organic layer is then separated and washed with water (2 × 50 ml) and the solvent is removed in vacuo. The remaining product **8** may be purified by recrystallization.

*2-Morpholinomethyl-1-(2-propynyl)-imidazole* (**8a**); yield: 91%; m.p. 78 °C (ether).

| | | | | |
|---|---|---|---|---|
| $C_{11}H_{15}N_3O$ | calc. | C 64.37 | H 7.37 | N 20.46 |
| (205.3) | found | 64.26 | 7.54 | 20.28 |

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.40 (t, 4H); 3.63 (t, 4H); 3.65 (s, 2H); 2.35 (t, $J$ = 2 Hz, 1H); 4.9 (d, $J$ = 2 Hz, 2H); 6.98 (d, $J$ = 1.5 Hz, 1H); 7.15 ppm (d, $J$ = 1.5 Hz, 1H).

*2-Morpholinomethyl-4,5-diphenyl-1-(2-propynyl)-imidazole* (**8b**); yield: 81%; m.p. 92 °C (benzene).

| | | | | |
|---|---|---|---|---|
| $C_{23}H_{23}N_3O$ | calc. | C 77.27 | H 6.49 | N 11.75 |
| (357.45) | found | 77.47 | 6.55 | 11.84 |

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.35 (t, $J$ = 2 Hz, 1H); 2.40 (t, 4H); 3.7 (t, 4H); 3.87 (s, 2H); 4.8 (d, 2H); 7.1–7.45 ppm (m, 10$H_{arom}$).

*2-Morpholinomethyl-1-(3-phenyl-2-propynyl)-imidazole* (**8c**); yield: 63%; m.p. 75 °C (ether).

| | | | | |
|---|---|---|---|---|
| $C_{17}H_{19}N_3O$ | calc. | C 72.56 | H 6.82 | N 14.93 |
| (281.4) | found | 72.33 | 6.99 | 14.75 |

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta$ = 2.42 (t, 4H); 3.75 (t, 4H); 3.80 (s, 2H); 5.22 (s, 2H); 6.95 (d, $J$ = 2 Hz, 1H); 7.12 ppm (d, $J$ = 2 Hz, 1H).

**7,7-(3-Oxa-1,5-pentanediyl)-7,8-dihydroimidazo[1,2-*a*]pyrazinium Perchlorates (9); Cyclization Procedure A:**
A solution of the 1-(2-alkynyl)-2-morpholinomethylimidazole (**8**; 0.1 mol) in methanol/water (50/50; 120 ml) is stirred at 50 °C for 2 h. Methanol is then distilled off in vacuo and the residual mixture is extracted with dichloromethane (3 × 30 ml). The aqueous layer is neutralized with perchloric acid (d = 1.67) and the precipitated perchlorate **9** is isolated by suction. The dichloromethane layer contains the corresponding imidazo[1,2-*a*]pyridine (**10**) and some unreacted educt **8**.

**Imidazo[1,2-*a*]pyridines (10); Cyclization Procedure B:**
A solution of the 1-(2-alkynyl)-2-morpholinomethylimidazole (**8**; 0.1 mol) in methanol/water (50/50; 120 ml) is refluxed for 5 h. Methanol is then distilled off in vacuo and the residual mixture is extracted with dichloromethane (3 × 30 ml). The aqueous layer is neutralized with perchloric acid (d = 1.67) and the precipitated perchlorate **9** is isolated by suction. The dichloromethane layer is dried with sodium sulfate and evaporated and the residual product **10** is purified by distillation in vacuo (**10a**) or by recrystallization (**10b, c**).

*Imidazo[1,2-a]pyridine* (**10a**) may also be obtained from perchlorate **9a** by heating **9a** (15.3 g, 0.05 mol) in aqueous sodium hydroxide (d = 1.38; 15 ml)/methanol (5 ml) for 2 h; yield: 4.25 g (72%).

**1-Allenyl-2-morpholinomethylimidazole (11a):**
1-(2-Propynyl)-2-morpholinomethylimidazole (**9a**; 30.6 g, 0.1 mol) is

**Table.** 7,7-(3-Oxa-1,5-pentanediyl)-7,8-dihydroimidazo[1,2-*a*]pyrazinium Perchlorates (**9**) and Imidazo[1,2-*a*]pyridines (**10**)

| Product | Yield [%] by Procedure A | Yield [%] by Procedure B | b.p./torr or m.p. [°C] (solvent) | Molecular formula[a] or Lit. Data | I.R. (KBr) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. (solvent/$TMS_{int}$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|
| **9a**[b] | 73 | 12 | m.p. 220° (isopropanol) | $C_{11}H_{16}ClN_3O_5$ (305.8) | 1690 | (DMSO-$d_6$): 2.45 (s, 3H); 3.45 (m, 4H); 4.25 (m, 4H); 5.60 (s, 2H); 7.65 (m, 2H); 7.20 (s, 1H) |
| **9b** | 84 | 5 | m.p. 250° (dec) (methanol) | $C_{23}H_{24}ClN_3O_5$ (457.9) | 1695 | (DMSO-$d_6$): 2.38 (s, 3H); 3.50 (m, 4H); 4.32 (m, 4H); 5.75 (s, 2H); 7.22 (s, 1H); 7.45–7.8 (m, 10H) |
| **9c** | 68 | 0 | m.p. 214° (methanol) | $C_{17}H_{20}ClN_3O_5$ (381.85) | 1690 | (DMSO-$d_6$): 3.45 (m, 4H); 4.30 (m, 4H); 5.60 (s, 2H); 5.85 (s, 2H); 7.15–7.35 (m, 8H) |
| **10a** | 5 | 82 | b.p. 96°/0.4 | b.p. 114°/3[10] | 1625 | ($CDCl_3$): 6.65 (t, $J$ = 5 Hz, 1H); 6.95 (m, 1H); 7.45 (m, 3H); 8.06 (d, $J$ = 5 Hz, 1H) |
| **10b** | 10 | 75 | m.p. 149° (acetone/ether) | m.p. 151°[11] | 1620 | ($CDCl_3$): 6.70 (t, $J$ = 5 Hz, 1H); 7.12–7.30 (m, 12H); 8.03 (d, $J$ = 5 Hz, 1H) |
| **10c** | 12 | 55 | m.p. 84° (ether) | $C_{13}H_{10}N_2$ (194.25) | 1620 | ($CDCl_3$): 6.63 (d, $J$ = 5 Hz, 1H); 7.1–7.35 (m, 7H); 8.05 (d, $J$ = 5 Hz, 1H) |

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.32; H, ±0.17; N, ±0.23.

[b] $^{13}$C-N.M.R. (DMSO-$d_6$/TMS): $\delta$ = 13.91 (q); 51.67 (t); 56.14 (t); 59.30 (t); 118.10 (d); 118.79 (d); 129.69 (d); 130.24 (s); 135.51 ppm (s).

stirred in aqueous sodium hydroxide (d = 1.38; 30 ml)/methanol (15 ml) for 2 h at room temperature. The mixture is then diluted with water (300 ml) and extracted with dichloromethane (2 × 50 ml). The organic extract is dried with sodium sulfate and the solvent evaporated. The residual crude product **11a** is purified by column chromatography on silica gel using ethyl acetate as eluent; yield: 11.9 g (58%); oil.

| | | | | |
|---|---|---|---|---|
| $C_{11}H_{15}N_3O$ | calc. | C 64.37 | H 7.37 | N 20.46 |
| (205.3) | found | 64.21 | 7.48 | 20.28 |

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 2.47 (t, 4H); 3.63 (t, 4H); 3.65 (s, 2H); 5.50 (d, 2H); 7.00 (d, 1H); 7.10 (d, 1H); 7.45 ppm (t, 1H).

The whole sequence **1–10** (or **1–11a**) may also be performed without purification of the intermediate products.

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