Facile Syntheses of 2-Ethenyl-1*H*-imidazoles

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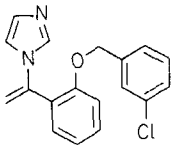
2-Ethenyl-1*H*-imidazoles **6** were readily prepared by treating 2-(1-hydroxyalkyl)-1*H*-imidazoles **5** with hot acetic anhydride. Several convenient procedures to precursors of **6** are described.

1-Methyl-2-vinyl-1*H*-imidazole (**6**, $R^1 = R^2 = R^3 = H$) is the monomer generally used for the preparation of interesting imidazole-containing polymers.[1] We required



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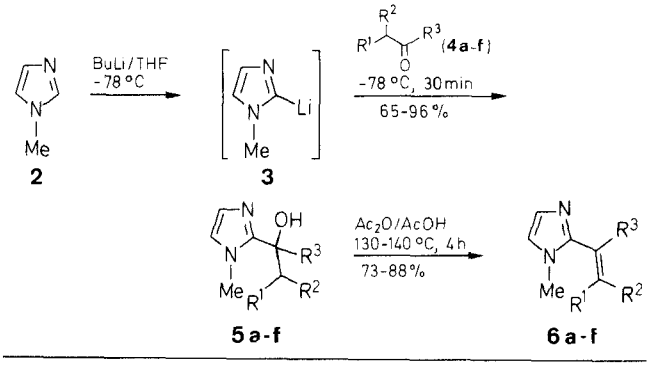
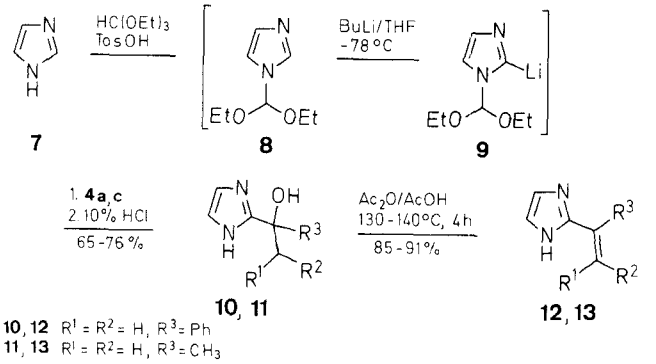
the synthesis of 2-ethenyl-1*H*-imidazole derivatives **6**, as possible anti-eubacterial agents related to cloconazole (**1**), a well known anti-eubacterial agent containing a 1-ethenyl-1*H*-imidazole moiety.

We report here several convenient procedures for facile synthesis of 2-ethenyl-1*H*-imidazoles **6**. The precursors, 2-(hydroxyalkyl)-1-methyl-1*H*-imidazoles **5a–f** were prepared by a known procedure, in which 2-lithio-1-methyl-1*H*-imidazole (**3**) was treated with an appropriate ketone **4**.[2,3] A solution of the tertiary alcohols **5a–f** in acetic anhydride/acetic acid was heated to give readily the corresponding olefinic compounds **6a–f** in high yield (Scheme **A**) (Table 1).



4–6	R^1	R^2	R^3
a	H	H	Ph
b	H	$-(CH_2)_5-$	
c	H	H	CH_3
d	CH_3	CH_3	i-C_3H_7
e	H	H	2-furyl
f	H	H	2-thienyl

Scheme A

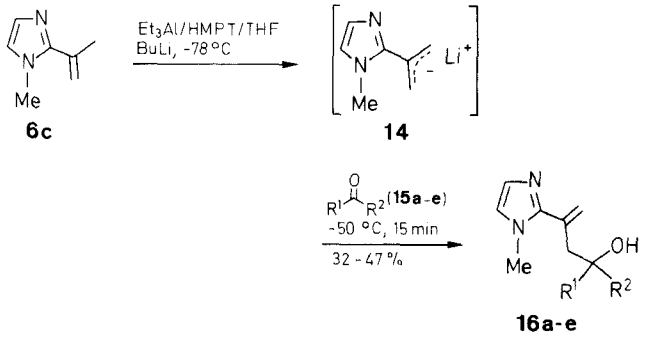


10, 12 $R^1 = R^2 = H$, $R^3 = Ph$
11, 13 $R^1 = R^2 = H$, $R^3 = CH_3$

Scheme B

1-Unsubstituted 2-ethenyl-1*H*-imidazoles **10** and **11** were prepared starting from imidazole **(7)** in a similar manner, except that the 1,1-diethoxymethyl group was used as an NH protecting group[3,4] (Scheme **B**) (Table 2).

Proton abstraction from the allyl group of 1-methyl-2-(1-propen-2-yl)-1*H*-imidazole **(6c)** by butyllithium proceeded successfully in the presence of hexamethylphosphoric triamide (HMPT) and triethylaluminum, and the resultant carbanion **14** was treated with several carbonyl compounds to give the corresponding hydroxyethenyl compounds **16a–e** in moderate yields (Scheme **C**) (Table 2).



15, 16	R^1	R^2	15, 16	R^1	R^2
a	H	H	**d**	H	
b	$-(CH_2)_5-$				
c	CH_3	Ph	**e**	Ph	Ph

Scheme C

Table 1. 2-Hydroxyalkyl-1H-imidazoles **5a–f**, **10** and **11** Prepared

Product	Typical Procedure	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	IR ($CHCl_3$) ν_{OH} (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
5a	A	88	151–152	151–152[2]	3170	1.82 (s, 3H, CH_3), 3.25 (s, 3H, NCH_3), 6.04 (s, 1H, OH), 6.79 (d, $1H_{imidazole}$, $J = 1$), 7.00 (d, $1H_{imidazole}$, $J = 1$), 7.00–7.45 (m, $5H_{arom}$)
5b	A	85	179–180	$C_{10}H_{16}N_2O$ (180.2)	3100	1.40–2.16 (m, 10H, CH_2), 2.43 (s, 1H, OH), 3.82 (s, 3H, NCH_3), 6.73 (d, $1H_{imidazole}$, $J = 1$), 6.82 (d, $1H_{imidazole}$, $J = 1$)
5c	A	96	130–131	$C_7H_{12}N_2O \cdot 0.25H_2O$ (144.7)	3100	1.65 (s, 6H, CH_3), 3.03 (s, 1H, OH), 3.83 (s, 3H, NCH_3), 6.70 (d, $1H_{imidazole}$, $J = 1$), 6.73 (d, $1H_{imidazole}$, $J = 1$)
5d	A	78	120–121	$C_{11}H_{20}N_2O$ (196.3)	3100	0.77, (d, 6H, CH_3, $J = 1$), 0.88 (d, 6H, CH_3, $J = 1$), 2.01–2.67 (m, 2H, CH), 2.60 (s, 1H, OH), 3.82 (s, 3H, NCH_3), 6.70 (d, $1H_{imidazole}$, $J = 1$), 6.93 (d, $1H_{imidazole}$, $J = 1$)
5e	A	87	173–174	$C_{10}H_{12}N_2O_2$ (192.2)	3100	1.87 (s, 3H, CH_3), 3.55 (s, 3H, NCH_3), 6.00 (s, 1H, OH), 6.20 (d, $1H_{furyl}$, $J = 3$), 6.38 (dd, $1H_{furyl}$, $J = 2$, 3), 6.73 (d, $1H_{imidazole}$, $J = 1$), 7.10 (d, $1H_{imidazole}$, $J = 1$), 7.50 (d, $1H_{furyl}$, $J = 2$)
5f	A	83	191–192	$C_{10}H_{12}N_2OS$ (208.3)	3080	1.92 (s, 3H, CH_3), 3.45 (s, 3H, NCH_3), 6.24 (s, 1H, OH), 6.50–7.10 (m, 4H, imidazole H + thiophene H), 7.34 (dd, $1H_{thiophene}$, $J = 1$, 6)
10	C	76	176–177	$C_{11}H_{12}N_2O$ (188.2)	3300	1.81 (s, 3H, CH_3), 5.90 (s, 1H, OH), 6.85 (s, $2H_{imidazole}$), 7.00–7.50 (m, $5H_{arom}$), 11.50 (br, 1H, NH)
11	C	65	203–204	$C_6H_{10}N_2O$ (126.2)	3150	1.45 (s, 6H, CH_3), 5.15 (s, 1H, OH), 6.80 (s, $2H_{imidazole}$), 11.55 (br, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.32, N ±0.36 (exceptions **5b**, N −0.59; **5c**, N −0.41).

Unfortunately, the 2-ethenyl-1*H*-imidazoles **6a–f** and **14a–e** synthesized did not have any significant antieubacterial activity.

All reagents except for Et_3Al in hexane were of commercial quality from freshly opened containers and purchased from Aldrich, Naclai or Wako. Et_3Al in hexane stored in special vialtype container was purchased from Tokyo Kasei.

Column chromatography was performed on Merck Kieselgel Art. 7747. The following instruments were used: ^{1}H-NMR spectra: Varian CFT-25 spectrometer, IR spectra: were obtained using a Shimadzu IR-410 spectrophotometer, MS: were obtained using a Hitachi M-80 spectrometer.

2-[(2-Furyl)-1-hydroxyethyl]1-methyl-1*H*-imidazole (5e); Typical Procedure A:

A 1.6 M solution of BuLi in hexane (6.25 mL, 10 mmol) is added at −78 °C under N_2 atmosphere to a solution of 1-methyl-1*H*-imidazole (**2**; 0.8 mL, 10 mmol), and the mixture is stirred for 10 min. 2-Acetylfuran (**4e**; 1.0 mL, 10 mmol) is added, and the mixture is stirred for 30 min at −78 °C. Water (10 mL) and EtOAc (50 mL) are added to the mixture, the organic layer is separated and dried (Na_2SO_4). Removal of the solvent gives a crystalline residue, which is recrystallized from EtOAc to give white needles of **5e**; yield: 1.68 g (87%).

2-[1-(2-Furyl)-1-ethenyl]-1-methyl-1*H*-imidazole (6e); Typical Procedure B:

A solution of the alcohol **5e** (1.00 g, 5.2 mmol) in a mixture of Ac_2O (2.5 mL) and AcOH (5 mL) is refluxed for 4 h at 130–140 °C under N_2 atmosphere. The volatiles are evaporated under reduced pressure, and the residue is stirred for 10 min at r.t. in the presence of water (5 mL) and 2-*tert*-butylhydroquinone (BQ, 5 mg). The mixture is made basic by the addition of solid K_2CO_3 followed by extraction with EtOAc (50 mL), the organic layer is dried

Table 2. 2-Ethenyl-1*H*-imidazoles **6** and **14** Prepared

Product	Typical Procedure	Yield (%)	mp (°C) or bp (°C)/Torr	Molecular Formula or Lit. mp	IR ($CHCl_3$) $\nu_{C=C}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
6a	B	74	120/1	$C_{12}H_{12}N_2$ (184.2)	1620	3.40 (s, 3H, NCH_3), 5.60 (s, H, C=CH_2), 5.80 (s, 1H, C=CH_2), 6.85 (d, 1H$_{imidazole}$, J = 1), 7.10 (d, 1H$_{imidazole}$, J = 1), 7.20 (s, 5H$_{arom}$)
6b	B	88	135/3	$C_{10}H_{14}N_2$ (162.2)	1650	1.27–2.61 (m, 8H, CH_2), 3.67 (s, 3H, NCH_3), 5.83–6.07 (m, 1H, C=CH), 6.77 (d, 1H$_{imidazole}$, J = 1), 6.95 (d, 1H$_{imidazole}$, J = 1)
6c	B	86	85/3	–[b]	1635	1.13–2.33 (d, 3H, =CCH_3, J = 1), 3.73 (s, 3H, NCH_3), 5.20 (q, 1H, =CH_2, J = 1), 5.43 (q, 1H, =CH_2, J = 1), 6.83 (d, 1H$_{imidazole}$, J = 1), 7.01 (d, 1H$_{imidazole}$, J = 1)
6d	B	79	103/2	$C_{11}H_{18}N_2$ (178.3)	1660	0.40–1.50 [m, 6H, CH(CH_3)$_2$], 1.38 [s, 3H, C=C(CH_3)$_2$], 1.85 [s, 3H, C=C(CH_3)$_2$], 2.67–3.25 [m, 1H, C<u>H</u>(CH_3)$_2$], 3.45 (s, 3H, NCH_3), 6.83–7.00 (2d, each 1H$_{imidazole}$, J = 1)
6e	B	73	130/3	$C_{10}H_{10}N_2O$ (174.2)	1620	3.70 (s, 3H, NCH_3), 5.30 (s, 1H, C=CH_2), 6.03 (s, 1H, C=CH_2), 6.23 (d, 1H$_{furyl}$, J = 3), 6.35 (dd, 1H$_{furyl}$, J = 2, 3), 6.90 (d, 1H$_{imidazole}$, J = 1), 7.07 (d, 1H$_{imidazole}$, J = 1), 7.40 (d, 1H, J = 2)
6f	B	80	120/3	$C_{10}H_{10}N_2S$ (190.3)	1610	3.70 (s, 3H, NCH_3), 5.30 (s, 1H, C=CH_2), 5.90 (s, 1H, C=CH_2), 6.88 (br m, 2H$_{thiophene}$), 6.97 (d, 1H$_{imidazole}$, J = 1), 7.08 (d, 1H$_{imidazole}$, J = 1), 7.20 (d, 1H$_{thiophene}$, J = 2)
12	B	85	157–158	$C_{11}H_{10}N_2$ (170.2)	1620	5.47 (s, 1H, C=CH_2), 5.81 (s, 1H, C=CH_2), 7.05 (br, 2H$_{imidazole}$), 7.39–7.51 (m, 5H$_{arom}$), 12.10 (br, 1H, NH)
13	B	91	165–166	$C_6H_8N_2$ (108.1)	1640	2.15 (d, 3H, CH_3, J = 1), 5.09 (s, 1H, C=CH_2), 5.59 (s, 1H, C=CH_2), 7.05 (s, 2H$_{imidazole}$), 12.10 (br, 1H, NH)
16a	D	41	112/3	$C_{10}H_{16}N_2O$ (180.2)	1630	1.25 (s, 6H, CH_3), 2.63 (s, 2H, CH_2), 3.50–5.00 (br, 1H, OH), 3.73 (s, 3H, NCH_3), 5.33 (s, 1H, C=CH_2), 5.40 (s, 1H, C=CH_2), 6.83 (d, 1H$_{imidazole}$, J = 1), 6.96 (d, 1H$_{imidazole}$, J = 1)
16b	D	47	oil	$C_{13}H_{20}N_2O$ (220.3)	1615	1.00–1.95 (br m, 11H, CH_2 + OH), 2.65 (s, 2H, =CCH_2), 3.75 (s, 3H, NCH_3), 5.38, 5.40 (2d, 1H each, C=CH_2, J = 1.5), 6.80 (d, 1H$_{imidazole}$, J = 1), 6.94 (d, 1H$_{imidazole}$, J = 1)
16c	D	43	155/3	$C_{15}H_{18}N_2O$ (242.3)	1625	1.60 (s, 3H, CH_3), 2.95 (s, 2H, =CCH_2), 3.55 (s, 3H, NCH_3), 5.10 (s, 1H, C=CH_2), 5.20 (s, 1H, C=CH_2), 5.55 (br, 1H, OH), 6.75 (s, 1H$_{imidazole}$, J = 1), 6.95 (s, 1H$_{imidazole}$, J = 1), 7.13–7.60 (m, 5H$_{arom}$)
16d	D	32	oil	$C_{15}H_{16}N_2O_3$ (272.3)	1630	2.81 (s, 2H, =CCH_2), 3.68 (s, 3H, NCH_3), 4.86 (q, 1H, C<u>H</u>OH), J = 4.7), 5.20 (s, 1H, C=CH_2), 5.30 (s, 1H, C=CH_2), 5.00–6.50 (br, 1H, OH), 5.90 (s, 2H, OCH_2O), 6.71–6.90 (m, 3H$_{arom}$), 6.99 (d, 1H$_{imidazole}$, J = 1), 7.01 (d, 1H$_{imidazole}$, J = 1)
16e	D	30	112–113	$C_{20}H_{20}N_2O \cdot 0.75H_2O$ (317.9)	1630	3.48 (s, 5H, NCH_3, =CCH_2), 4.97 (s, H, C=CH_2), 5.03 (s, 1H, C=CH_2), 5.50–6.50 (br, 1H, OH), 6.74 (d, 1H$_{imidazole}$, J = 1), 6.98 (d, 1H$_{imidazole}$, J = 1), 7.16–7.51 (m, 10H$_{arom}$)

[a] Satisfactory microanalyses obtained: C ±0.21, H ±0.23, N ±0.34 (for **12**, **13** and **16e**). Compounds **6a–f** and **16a–d** gave exact mass in HRMS within ±0.002.

[b] Not reported in ref. 1.

(Na_2SO_4). Evaporation of the solvent under a reduced pressure in the presence of BQ (10 mg) gives an oil, which is distilled using a Kugelrohr apparatus in the presence of BQ (5 mg) in the receiver to give an pale yellow oil; yield: 0.66 g (73%); bp 130°C/3 Torr. In the absence of BQ, the product is readily polymerized.

2-(1-Hydroxy-1-phenylethyl)-1*H*-imidazole (10); Typical Procedure C:

A solution of imidazole (**7**; 680 mg, 10 mmol) in a mixture of $CH(OEt)_3$ (10 mL), benzene (25 mL) and TsOH (20 mg) is refluxed for 30 min under N_2 atmosphere, and then $CH(OEt)_3$ and benzene are evaporated. A solution of the residue in a mixture of $CH(OEt)_3$ (10 mL) and benzene (25 mL) is again refluxed for 30 min under removal of 10 mL of the distillate during the period. Removal of $CH(OEt)_3$ and the solvent under a reduced pressure gives a viscous residue, to a solution of which in THF (20 mL) 1.6 M BuLi in hexane (6.7 mL, 10.5 mmol) is added at −78°C under N_2 atmosphere. After being stirred for 15 min, acetophenone (**4a**; 1.17 mL, 10 mmol) is added dropwise, and then the mixture is stirred for 30 min. It is then treated with 10% HCl (10 mL) and stirred overnight. The mixture is made basic by the addition of solid K_2CO_3 followed by extraction with EtOAc (50 mL). Removal of the solvent after drying (Na_2SO_4) gives a crystalline residue, which is recrystallized from 2-propanol to give white needles of **10**; yield: 1.43 g (76%).

2-[(1-(1-Hydroxycyclohexyl)-2-propen-2-yl]-1-methyl-1*H*-imidazole (14b); Typical Procedure D:

A 15% hexane solution of Et_3Al (0.55 mL, 0.5 mmol) is added at −78°C under N_2 atmosphere to a solution of **6c** (1.22 g; 10 mmol), HMPT (1.74 mL, 10 mmol) and THF (20 mL), and then 1.6 M BuLi in hexane (6.4 mL, 10 mmol) is added. Cyclohexanone (**14b**; 1.05 mL, 10 mmol) is added slowly to the mixture after stirring for 10 min. The mixture is stirred for 15 min at −50°C followed by addition of sat. NH_4Cl (2 m) and H_2O (3 m), and the product is extracted with EtOAc. The organic layer is evaporated after drying (Na_2SO_4) to give a viscous oil of crude **14b**; which is purified by a column chromatography on silica gel (solvent: EtOAc/MeOH, 20:1); yield: 1.04 g (47%).

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