Enamines 43[1]. A Simple Synthesis of 4-Amino-4,5-dihydro-1*H*-imidazoles

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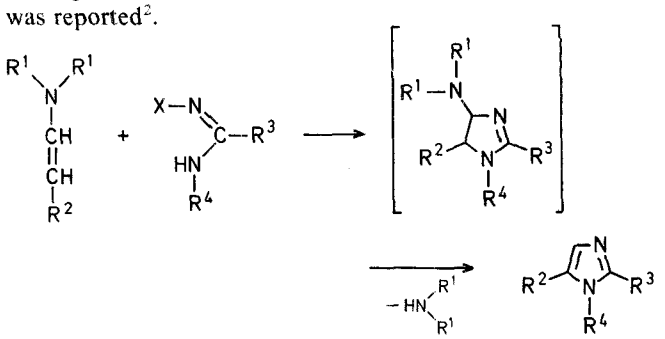
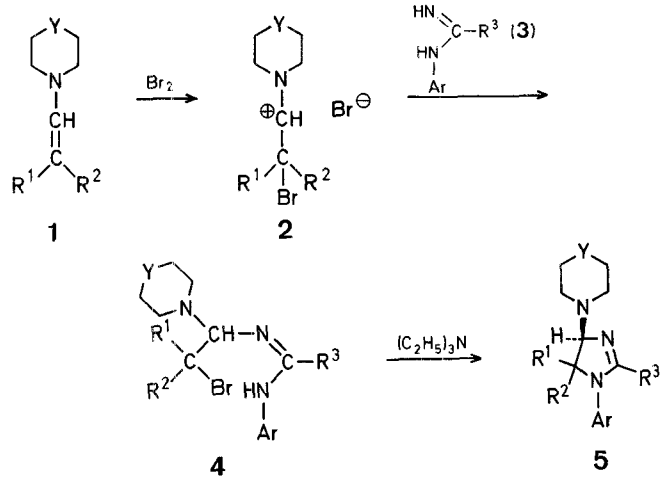
Some years ago, a new entry to the imidazole ring system involving the reaction of 1-aminoethenes with *N*-haloamidines was reported[2].



Although the formation of 4-amino-4,5-dihydro-1*H*-imidazoles as intermediates was shown, in all cases only the 1,2,5-trisubstituted imidazoles were isolated as a result of the instability of the 4-amino derivatives under the reaction conditions.

We now report a simple preparation of 4-amino-4,5-dihydro-1*H*-imidazoles **5** by reaction of the enamines **1** with amidines **3** in the presence of an equimolar amount of bromine. We assume that the bromine reacts with the enamine double bond to give the bromoimmonium intermediate **2** which is reactive towards the amidine nucleophilic nitrogen atoms. The intermediate **4** thus formed cyclizes to give the product **5**.



Beside the 4-aminoimidazolines **5**, small amounts of the 4-hydroxy-analogues **7** were isolated, mainly when the reaction medium was not strictly anhydrous. This fact, already observed in a similar reaction[3], can be explained by a partial hydrolysis of the reactive intermediate **2** followed by nucleophilic attack of the amidine on the α-bromo-aldehyde **6** thus formed.

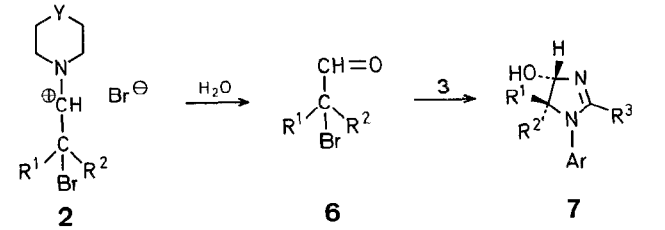


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Table 1. 4-Amino-4,5-dihydro-1*H*-imidazoles **(5a–j)** prepared

Product No.	R^1	R^2	R^3	Ar	Y	Yield [%]	m.p.[a] [°C] (solvent)	Molecular formula[b] or Lit. m.p.	^{1}H-N.M.R. ($CDCl_3$)[c] J_{H_4,H_5} [Hz]	δ_{H_4} and/or δ_{H_5} [ppm]
5a	H	C_6H_5	C_6H_5	C_6H_5	O	65	200–202° (isopropanol)	202°[2]	5	4.73, 4.71
5b	H	C_6H_5	C_6H_5	C_6H_5	—	35	173–175° (isopropanol)	$C_{25}H_{25}N_3$ (367.5)	4	4.87, 4.65
5c	H	C_6H_5	C_6H_5	C_6H_5	CH_2	50	178–179° (acetone)	$C_{26}H_{27}N_3$ (381.5)	4	4.75, 4.65
5d	H	C_6H_5	C_6H_5	2,6-di-Cl—C_6H_3	O	65	146–148° (diisopropyl ether)	$C_{25}H_{23}Cl_2N_3O$ (452.4)	[d]	5.30, 5.30
5e	H	C_6H_5	C_6H_5	4-H_3CO—C_6H_4	O	70	192–194° (isopropanol)	$C_{26}H_{27}N_3O_2$ (413.5)	4	4.70, 4.56
5f	H	C_6H_5	SCH_3	C_6H_5	O	85	139° (isopropanol)	$C_{20}H_{23}N_3OS$ (353.5)	4	4.80, 4.55
5g	H	C_6H_5	CH_3	C_6H_5	O	65	118–119° (diisopropyl ether)	$C_{20}H_{23}N_3O$ (321.4)	6	4.75, 4.53
5h	H	C_6H_5	C_6H_5	4-O_2N—C_6H_4	O	40	247° (methanol)	$C_{25}H_{24}N_4O_3$ (428.5)	4	4.80, 4.68
5i	CH_3	C_6H_5	C_6H_5	C_6H_5	O	60	182–184° (acetone)	182°[2]	—	4.52, —
5j	H	*n*-C_5H_{11}	C_6H_5	C_6H_5	O	40	oil	$C_{24}H_{31}N_3O$ (377.5)	4	4.52, [e]

[a] Uncorrected.
[b] The microanalyses were in good agreement with the calculated values: C, ±0.22; H, ±0.13; N, ±0.15.
[c] Recorded at 60 MHz on a Varian A 360 spectrometer.
[d] *J* not measurable.
[e] Masked by other signals.

Table 2. 4-Hydroxy-4,5-dihydro-1*H*-imidazoles **7a–d** prepared

Product No.	R^1	R^3	Ar	Yield [%]	m.p.[a] [°C] (solvent)	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$)[c] J_{H_4,H_5} [Hz]	δ_{H_4} [ppm]	δ_{H_5} [ppm]
7a	C_6H_5	C_6H_5	C_6H_5	45[d] (10.5)[e]	180°[f] (isopropanol)	$C_{21}H_{18}N_2O$ (413.4)	4	5.55	4.75
7b	C_6H_5	C_6H_5	4-H_3CO—C_6H_4	10[e]	157°[f] (isopropanol)	$C_{22}H_{20}N_2O_2$ (344.4)	4	5.55	4.65
7c	C_6H_5	C_6H_5	4-O_2N—C_6H_4	5[e]	210°[f] (methanol)	$C_{21}H_{17}N_3O_3$ (362.4)	3	5.38	4.85
7d	C_6H_5	C_6H_5	2,6-di-Cl—C_6H_3	10[e]	161–164°[f] (isopropanol)	$C_{23}H_{22}N_2O$ (342.4)	4	5.88	4.50

[a] Uncorrected.
[b] The microanalyses were in good agreement with the calculated values: C, ±0.29; H, ±0.13; N, ±0.2.
[c] Recorded at 60 MHz on a Varian A 360 spectrometer.
[d] From α-bromophenylacetaldehyde.
[e] As by-product beside the 4-amino-2-imidazolines **3**.
[f] With loss of water.

An authentic sample of α-bromophenylacetaldehyde (**6**; $R^1 = C_6H_5$, $R^2 = H$) reacts with *N*-phenylbenzamidine affording 4-hydroxy-1,2,5-triphenyl-4,5-dihydro-1*H*-imidazole **7a** in almost quantitative yield, thus confirming the hypothesis of the origin of the 4-hydroxy derivatives.

Amidines 3:
These compounds were prepared according to the methods reported[2].

Enamines 1:
2-Morpholino-, 2-pyrrolidino-, 2-piperidino-styrenes, 1-morpholinobutadiene, and 1-morpholinoheptene are known compounds and were prepared by reported methods[4,5,6].

4-Amino-4,5-dihydro-1*H*-imidazoles 5; General Procedure:
To a stirred solution of enamine **1** (20 mmol), amidine **3** (20 mmol) and triethylamine (5.7 ml, 40 mmol) in dry dichloromethane (100 ml) cooled to 0°C, bromine (3.2 g, 20 mmol) in dry dichloromethane (20 ml) is added dropwise under nitrogen. Stirring is continued for 30 min at room temperature. The mixture is washed with sodium hydrogen carbonate solution (40 ml). The organic layer is separated, dried with sodium sulphate, and freed from the solvent under reduced pressure to give the crude 4,5-dihydro-1*H*-imidazoles **5** which is purified by crystallization from a suitable solvent (Table 1).

4-Hydroxy-4,5-dihydro-1*H*-imidazoles 7; General Procedure:
The mother liquors from the crystallization of the 4-amino-4,5-dihydro-1*H*-imidazoles **3** are freed from the solvent under reduced pressure to give the crude 4-hydroxy-4,5-dihydro-1*H*-imidazoles **7** which are purified by column chromatography on silica gel (ratio silica gel/crude product 40 : 1) eluting with ethyl acetate/triethylamine (90 : 10) (Table 2).

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***trans*-1,2,5-Triphenyl-4-hydroxy-4,5-dihydro-1*H*-imidazole (7a):**
To a stirred solution of α-bromophenylacetaldehyde[7] (2 g, 10 mmol) in dry tetrahydrofuran (30 ml), *N*-phenylbenzamidine (2 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in dry tetrahydrofuran (30 ml) are added dropwise. After 30 min the solvent is removed under reduced pressure, the crude residue is treated with sodium hydrogen carbonate solution (20 ml), and extracted with dichloromethane (2 × 20 ml). The organic layer is separated, dried with sodium sulphate, and freed from the solvent under reduced pressure to give the crude *trans*-1,2,5-triphenyl-4-hydroxy-4,5-dihydro-1*H*-imidazole **4a** which is purified by column chromatography on silica gel (ratio silica gel/crude product = 40 : 1) eluting with ethyl acetate/triethylamine (80 : 20), followed by crystallization from diisopropyl ether (Table 2).

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