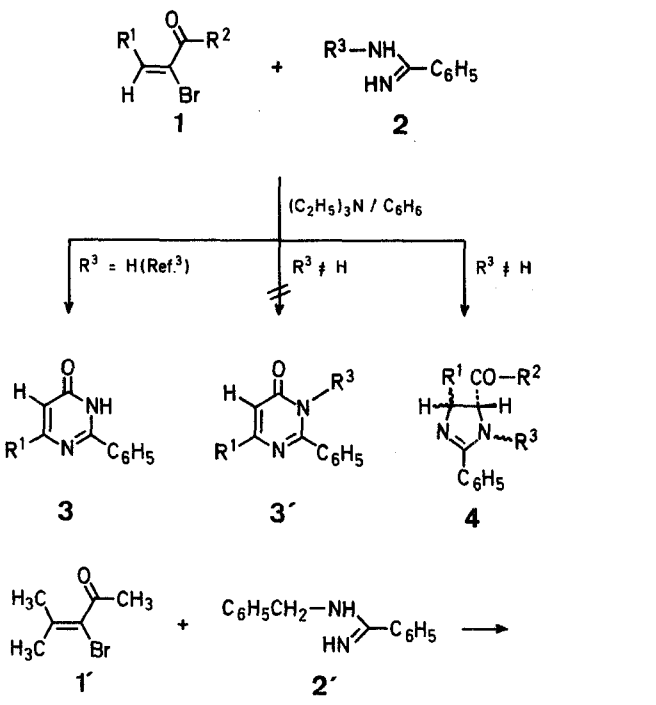
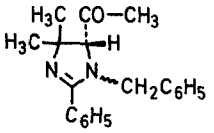


4	R^1	R^2	R^3
a	C_6H_5	OC_2H_5	CH_3
b	C_6H_5	OC_2H_5	i-C_3H_7
c	C_6H_5	OCH_3	$C_6H_5-CH_2$
d	C_6H_5	OC_2H_5	$C_6H_5-CH_2$
e	4-Cl-C_6H_4	OC_2H_5	i-C_3H_7
f	4-H_3C-C_6H_4	OC_2H_5	$C_6H_5-CH_2$
g	C_6H_5	C_6H_5	i-C_3H_7
h	C_6H_5	C_6H_5	$C_6H_5-CH_2$
i	C_6H_5	CH_3	$C_6H_5-CH_2$
j	C_6H_5	CH_3	i-C_3H_7
k	C_6H_5	t-C_4H_9	i-C_3H_7
l	C_6H_5	t-C_4H_9	$C_6H_5-CH_2$
m	C_6H_5	H	i-C_3H_7
n	C_6H_5	CN	i-C_3H_7



4'

New One-Step Synthesis of Functionalized 2-Imidazolines

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Among the syntheses of pyrimidinones[1,2,3], of interest in the medicinal chemistry field, we recently proposed a new route to 2,6-disubstituted 4(3*H*)-pyrimidinones **3**[4]. This synthesis is performed by reacting unsubstituted amidines with 2-bromo-2-alkenoic esters. We report here a one step synthesis of functionalized 2-imidazolines **4** and **4'**. This heterocycle was formed when 2-bromo-2-alkenoic esters **1** were allowed to react with mono-substituted amidines **2**. The expected trisubstituted pyrimidinones **3'** were not obtained. Ketones, aldehydes and nitriles were also able to take the place of esters in this ring formation.

All reactions were performed in benzene with triethylamine as catalyst. The temperature of 0 °C must be maintained during the addition of the amidine reagent. Under the above conditions, our method fails with acetamidine, *N,N*-dimethylbenzamidine, *N*-*t*-butylbenzamidine, guanidine, and *O*-methylisourea. These observations were closely related with increased steric hindrance at the nitrogen atom of the amidines (Table).

Spectral data of compounds **4** and **4'** were consistent with the proposed structures. Typical ^{1}H-N.M.R. coupling constants and ^{13}C-N.M.R. chemical shifts, characteristic of 2-imidazolines are observed. The compounds **4** exhibit a typical AB pattern. The coupling constant observed for the vicinal protons, $J_{H\text{-}4,H\text{-}5}$, for a *cis*-configuration, is always larger than the coupling constant for a *trans*-configuration[5] (Table). These observations are consistent with the results reported in the literature[6,7,8].

We reported[4] that, in the reaction of **1** with **2**, when the substituent R^3 in the amidines **2** is hydrogen, the compounds **3** were obtained exclusively. However, in the literature[2,3,9], similar reactions were reported to give **3**, when carried out using unsubstituted or *N*-substituted amidines. These experimental features suggest that our reaction follows a different pathway. In this case, several mechanisms can be advanced for the formation of **4** and **4'** and at the same time for 4(3*H*)-pyrimidinones **3**.

Here, the best analogy was found in the condensation of primary amines with ethyl 2-bromocinnamate[10,11], which allows us to propose a mechanism via an aziridine and a 2-oxo-1,3-diazabicyclo[3.1.0]hexene system as intermediates. The isolation of such very unstable species was unsuccessful under the conditions of reaction. This result is not a surprise as it is known that the same problem was encountered in the literature[12–15].

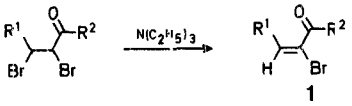
Finally, when the substituent R^3 in amidine **2** is other than hydrogen, the formation of 2-imidazolines **4** can be explained by earlier observations reported in the literature[16,17]. We have noted also that the stereochemistry obtained for our compounds **4** was consistent with the stereospecificity and regiospecificity observed earlier in the rearrangement of the aziridines[16,17] into 2-imidazolines or 2-oxazolines.

The reaction reported here has the following advantages:

- It is the first known direct synthesis of such functionalized 2-imidazolines.
- The reaction takes place under mild conditions. It is regiospecific and stereospecific with ketones or nitriles. A high stereoselectivity is observed with some esters.

The starting materials **1**, **1'**, and **2** were prepared by adaptions of known procedures[18,19].

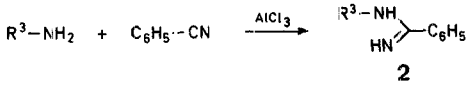
1-Aryl-2-bromo-3-oxo-1-alkenes 1 and 2-Methyl-3-bromo-4-oxo-2-pentene (1'); General Procedure:



1

To the appropriate 2,3-dibromoalkanoic compound (0.2 mol) dissolved in chloroform (200 ml), triethylamine (22.3 g, 0.22 mol) is added dropwise. The mixture is stirred for 4 h at room temperature. Triethylamine hydrobromide is then filtered off. The filtrate is evaporated and the residual product distilled under reduced pressure (0.1 torr). In the case of solids, they are used directly without further purification.

***N*-Substituted Amidines 2; General Procedure:**



2

To a mixture of the appropriate amine (0.1 mol) and benzonitrile (0.1 mol), anhydrous aluminium chloride (16.0 g, 0.12 mol) is added slowly (exothermic reaction) under vigorous stirring. After cooling to room temperature, the solid is hydrolysed with distilled water (200 ml or more) in an ice bath (exothermic). The aqueous phase is washed with ether (2 × 20 ml), and made alkaline with 50% sodium hydroxide solution (100 ml). The solution is extracted with ether

Table. 2-Imidazolines **4a–n** and **4'** prepared

Product No.	Yield[a] [%]	*cis*/*trans* ratio		m.p. [°C][b] (solvent)	Molecular formula[c]	I.R. (Film) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS)[d,e] δ [ppm]	^{13}C-N.M.R. (CDCl$_3$/TMS)[d,e] δ [ppm]	MS (70 eV)[f] *m/e*
		cis	*trans*						
4a	10	90	10[g]	oil	$C_{19}H_{20}N_2O_2$ (308.4)	1750 (C=O), 1630 (C=N)	*cis*: 0.90 (t, 3H, J = 7 Hz); 2.90 (s, 3H); 3.70 (q, 2H, J = 7 Hz); 4.50 (d, 1H, J = 12 Hz); 5.50 (d, 1H, J = 12 Hz); 7.0–8.0 (m, 10H)	–	–
4b	40	50	50[g]	oil	$C_{21}H_{24}N_2O_2$ (336.4)	1755 (C=O), 1630 (C=N)	*cis*: 0.90 (t, 3H, J = 8 Hz); 1.05 (d, 3H, J = 9 Hz); 1.20 (d, J = 9 Hz); 3.65 (q, 2H, J = 8 Hz); 3.95 (sept, 1H, J = 8 Hz); 4.70 (d, 1H, J = 12 Hz); 7.20–7.80 (m, 10H) *trans*: 0.83 (d, 3H, J = 5 Hz); 1.07 (d, 3H, J = 5 Hz); 1.30 (t, 3H, J = 8 Hz); 3.90 (sept, 1H, J = 5 Hz); 4.90 (d, 1H, J = 7 Hz); 4.20 (q, 2H, J = 8 Hz); 5.19 (d, 1H, J = 7 Hz); 7.20–7.90 (m, 10H)	13.61, 14.22, 19.25, 19.65, 21.55, 21.80, 29.27, 47.75, 47.95, 60.51, 61.23, 63.07, 66.21, 72.77, 73.10, 126–130.21, 131.21, 138.90, 143.70, 167.04, 167.70, 171.23, 173.79	*cis*: 336 (M^+), 335, 334, 293, 292, 263, 247, 246, 220, 218, 210, 193, 144, 118, 116, 115, 105 *trans*: 336 (M^+), 335, 334, 293, 263, 221, 193, 160, 117, 105, 91
4c	22	95	5[g]	oil	$C_{24}H_{22}N_2O_2$ (370.4)	1750 (C=O), 1625 (C=N)	*cis*: 3.12 (s, 3H); 4.15 (d, 1H, J = 15 Hz); 4.48 (d, 1H, J = 12 Hz); 4.74 (d, 1H, J = 15 Hz); 5.52 (d, 1H, J = 12 Hz); 7.0–8.0 (m, 15H)	–	*cis*: 370 (M^+), 369, 368, 311, 279, 211, 210, 193, 178, 121, 105, 91

Table. (Continued)

Product No.	Yield[a] [%]	*cis*/*trans* ratio *cis*	*trans*	m.p. [°C][b] (solvent)	Molecular formula[c]	I.R. (Film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d,e] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS)[d,e] δ [ppm]	MS (70 eV)[f] *m/e*
4d	14	61	39[h]	oil	$C_{25}H_{24}N_2O_2$ (384.4)	1750 (C=O), 1630 (C=N)	*cis*: 0.80 (t, 3H, J = 6 Hz); 3.58 (q, 2H, J = 6 Hz); 4.18 (d, 1H, J = 15 Hz); 4.48 (d, 1H, J = 12 Hz); 4.75 (d, 1H, J = 12 Hz); 5.52 (d, 1H, J = 12 Hz); 7.0–8.0 (m, 15H) *trans*: 1.26 (t, 3H, J = 6 Hz); 4.51 (d, 1H, J = 7 Hz); 5.07 (q, 2H, J = 6 Hz); 5.31 (d, 1H, J = 7 Hz); 7.0–8.0 (m, 15H)	–	*cis*: 384 (M^+), 383, 382, 311, 293, 211, 210, 193, 117, 105, 91 *trans*: 384, 382, 311, 293, 291, 225, 219, 211, 210, 193, 122, 121, 105, 104, 91
4e	38	75	25[i]	oil	$C_{21}H_{23}ClN_2O_2$ (370.9)	1750 (C=O), 1630 (C=N)	*cis*: 0.80 (d, 3H, J = 6 Hz); 0.93 (t, 3H, J = 8 Hz); 3.47 (g, 2H, J = 8 Hz); 3.65 (sept, 1H, J = 4 Hz); 4.64 (d, 1H, J = 12 Hz); 5.63 (d, 1H, J = 12 Hz); 7.26 (d, 2H, J = 11 Hz); 7.48 (m, 4H); 7.74 (m, 2H) *trans*: 1.35 (t, 3H, J = 8 Hz); 3.9 (sept, 1H, J = 4 Hz); 4.04 (d, 1H, J = 7 Hz); 4.31 (q, 2H, J = 8 Hz); 5.17 (d, 1H, J = 7 Hz); 7.26 (d, 2H, J = 11 Hz); 7.48 (m, 4H); 7.74 (m, 2H)	–	–
4f	7	60	40[i]	oil	$C_{26}H_{24}N_2O_2$ (396.5)	1750 (C=O), 1630 (C=N)	*cis*: 0.81 (t, 3H, J = 7 Hz); 2.30 (s, 3H); 5.51 (d, 1H, J = 12 Hz); 7.0–8.0 (m, 14H) *trans*: 1.29 (t, 3H, J = 7 Hz); 2.33 (s, 3H); 5.24 (d, 1H, J = 12 Hz); 7.0–8.0 (m, 14H)	–	–
4g	46	0	100[g]	118° (ether)	$C_{25}H_{24}N_2O$ (368.4)	1750 (C=O)[j], 1620 (C=N)	*trans*: 0.98 (d, 6H, J = 8 Hz); 4.0 (sept, 1H, J = 8 Hz); 4.87 (d, 1H, J = 7 Hz); 5.15 (d, 1H, J = 7 Hz); 7.20–7.80 (m, 15H)	19.48, 20.90, 47.91, 70.82, 73.34, 131.25, 133.48, 143.70, 167.24, 199.58	263, 223, 149, 122, 105, 84
4h	23	0[g]	100	50° (ether)	$C_{29}H_{24}N_2O$ (416.5)	1755 (C=O), 1630 (C=N)	*trans*: 4.26 (d, 1H, J = 15 Hz); 4.69 (d, 1H, J = 15 Hz); 4.87 (d, 1H, J = 7 Hz); 5.07 (d, 1H, J = 7 Hz); 7.0–8.0 (m, 20H)	50.80, 72.82, 72.93, 133.50, 136.29, 134.63, 143.68, 165.91, 197.25	414, 311, 225, 122, 105, 91, 89

Table. (Continued)

Product No.	Yield[a] [%]	*cis*/*trans* ratio		m.p. [°C][b] (solvent)	Molecular formula[c]	I.R. (Film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d,e] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS)[d,e] δ [ppm]	MS (70 eV)[f] *m/e*
		cis	*trans*						
4i	33	0	100[g]	oil	$C_{24}H_{22}N_2O$ (354.4)	1720 (C=O), 1620 (C=N)	*trans*: 2.13 (s, 3H); 4.01 (d, 1H, J = 7 Hz); 4.29 (q, 2H, J = 12 Hz); 5.07 (d, 1H, J = 7 Hz); 7.0–8.0 (m, 15H)	26.19, 52.04, 72.15, 77.40, 130.67, 136.04, 143.12, 166.51, 209.69	353, 193, 105, 91, 89
4j	30	0	100[g]	oil	$C_{20}H_{22}N_2O$ (306.4)	1720 (C=O) 1620 (C=N)	*trans*: 0.38 (d, 3H, J = 6 Hz); 0.66 (d 3H, J = 6 Hz); 2.02 (s, 3H); 3.61 (sept, 1H, J = 6 Hz); 3.97 (d, 1H, J = 7 Hz); 7.13–7.67 (m, 8H); 7.70–7.74 (m, 2H)	19.27, 21.96, 25.06, 48.18, 72.38, 73.72, 131.56, 143.46, 166.25, 209.55	304, 264, 263, 221, 193, 160, 145, 118
4k	18	0	100[g]	141–142° (ether)	$C_{23}H_{28}N_2O$ (348.5)	1715 (C=O), 1600 (C=N)	*trans*: 0.69 (d, 3H, J = 7 Hz); 0.83 (d 3H, J = 7 Hz); 1.02 (s, 9H); 3.86 (sept, 1H, J = 7 Hz); 4.64 (d, 1H, J = 5.5 Hz); 5.02 (d, 1H, J = 5.5 Hz); 7.08–7.35 (m, 8H); 7.69 (m, 2H)	20.62, 22.35, 27.59, 44.00, 47.32, 66.63, 73.01, 131.11, 142.93, 166.31, 212.79	–
4l	9	0	100[g]	oil	$C_{27}H_{28}N_2O$ (396.5)	1710 (C=O), 1620 (C=N)	*trans*: 0.95 (s, 9H); 4.22 (d, 1H, J = 16 Hz); 4.50 (d, 1H, J = 16 Hz); 4.48 (d, 1H, J = 5.5 Hz); 7.06 (m, 13H); 7.50 (m, 2H)	26.29, 43.74, 50.61, 70.42, 73.21, 130.90, 136.69, 142.35, 166.12, 211.90	–
4m	10	–[k]		oil	$C_{19}H_{20}N_2O$ (292.4)	3440 (OH), 1715 (C=O), 1600 (C=N)	1.29 (m, 6H); 3.63 (sept, 1H, J = 7 Hz); 3.62 (s, 1H); 4.44–5.55 (m, 2H); 7.0–8.2 (m, 10H); 9.35 (s, 1H)	–	–
4n	3	0	100[g]	100–101° (PE)	$C_{19}H_{19}N_3$ (289.4)	2240 (C≡N), 1640 (C=N)	*trans*: 0.86 (d, 3H, J = 6 Hz); 1.36 (d 3H, J = 6 Hz); 4.0 (sept, 1H, J = 6 Hz); 4.85 (d, 1H, J = 7 Hz); 5.5 (d, 1H, J = 7 Hz); 7.35–7.65 (m, 12H)	–	–
4'	16	–[k]		88° (pentane)	$C_{20}H_{22}N_2O$ (306.4)	1730 (C=O), 1630 (C=O)	1.2 (s, 3H); 1.4 (s, 3H); 2.1 (s, 3H); 3.7 (s, 1H); 4.01 (d 1H, J = 15 Hz); 4.70 (d, 1H, J = 15 Hz); 6.90–7.70 (m, 10H)	–	264, 263, 249 172, 160, 145 104, 91

[a] Yield of isolated product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.25, N ± 0.31.
[d] Recorded on a Bruker WP 100 MHz spectrometer.
[e] ^{1}H- and ^{13}-N.M.R. assignments are available on request to the authors.
[f] Recorded on a AEI MS 30 mass spectrometer.
[g] Separated by preparative T.L.C. on silica gel.
[h] Separated by H.P.L.C. on lichrosorb Si 60 (5m, Merck).
[i] Determined by integration of NMR signals.
[j] KBr pellet.
[k] Undetermined.

(300 ml). The organic layer is dried with anhydrous potassium carbonate and the amidine base is precipitated by bubbling gaseous hydrogen chloride. The obtained amidine hydrochloride obtained is pure enough for further use.

N-Methylbenzamidine (**2**; $R^3 = CH_3$) is prepared according to Refs.[20,21].

2,4-Diphenyl-2-imidazolines 4a–n and 4′; General Procedure:
To a solution of the appropriate compound **1** or **1′** (0.1 mol) in anhydrous benzene or chloroform (20 ml) is added dropwise a mixture of the amidine base **2** (0.12 mol) and triethylamine (10.1 g, 0.1 mol) in 15 min at 0 °C. The ice bath is removed at the end of the addition and the mixture is stirred for 6 h at room temperature. The mixture is then refluxed for 30 min to complete the reaction. The triethylammonium bromide is filtered off and the solvent is evaporated in vacuo below 40 °C. The crude product is purified by column chromatography on silica gel or by preparative T.L.C. on silica gel.

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