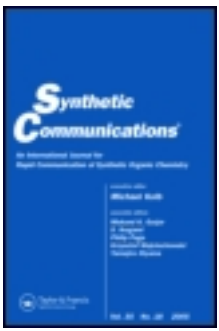

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Synthesis of Heterocyclic Ketene Aminals with a β-Hydroxyethyl Group on the Nitrogen Atom

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Synthesis of Heterocyclic Ketene Aminals with a β-Hydroxyethyl Group on the Nitrogen Atom

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Abstract: The heterocyclic ketene aminals **4** with a β-hydroxyethyl group on the nitrogen atom are synthesized by the reaction of the corresponding ketene mercaptals **3** with 2-(2-aminoethylamino)ethanol. In the case of **3** with one aroyl substituent, besides the ketene aminals **4,** the benzoate of ketene aminals **5** are also isolated.

Heterocyclic ketene aminals are important synthon for the synthesis of a wide variety of new heterocycles and fused heterocycles, therefore, their synthesis and reactions have given rise to much attention.[1] Although heterocyclic ketene aminals with various substituents have been synthesized, however, the synthesis of heterocyclic ketene aminals with a functional group on the nitrogen atom was fewer reported. We consider that heterocyclic ketene aminals with a functional group, such as

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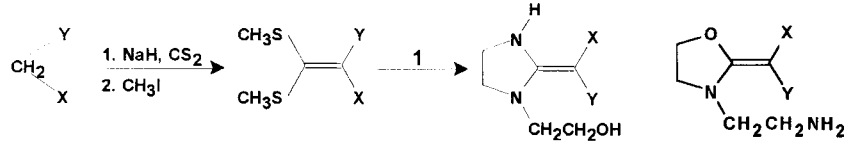
hydroxyethyl group, on the nitrogen atom will change or enhance their biological activities, as in some pyrimidine acyclonucleosides[2,3]. Here we wish to report the results of synthesis of heterocyclic ketene aminals with a β-hydroxyethyl group on the nitrogen atom.

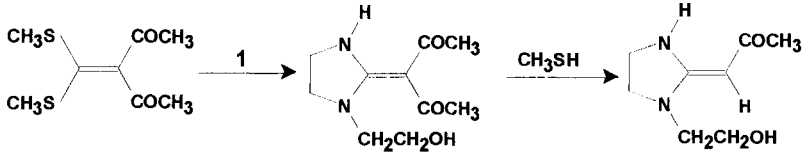
We use 2-(2-aminoethylamino)ethanol (**1**) as starting material to react with ketene mercaptals **3** for the synthesis of *N*-(β-hydroxyethyl) substituted heterocyclic ketene aminals. The ketene mercaptals **3** are prepared by the reaction of the corresponding active methylene compounds **2** with sodium hydride and carbon disulfide followed by treatment with methyl iodide in a one-pot reaction. When the X and Y of **3** are both electron-withdrawing groups or the one is nitro group, **3a-g** react easily with **1** at room temperature (with the exception of **3e**) to give the products in good to excellent yields. From the elemental analyses and the mass spectral data, the constitution of the reaction products may be ketene aminals **4a-g** or ketene *N,O*-acetals **A**. In our previous paper[4], it is shown that 2-aminoethanol reacted with ketene mercaptals is much slower than that of 1,2-ethanediamine. And also from the ^{1}H-NMR data of the reaction products, two deuterium exchangable proton signals appear at the region of 7.82-9.83 ppm (assigned as NH) and the region of 4.44--4.90 ppm (assigned as OH). These facts indicate that the structure of the reaction products is ketene aminals **4** and not the ketene *N,O*-acetals **A**.



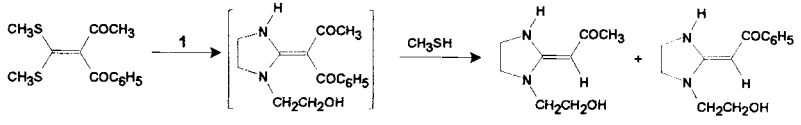
2 **3a-g** **4a-g** **A**

2-4	a	b	c	d	e	f	g
X	NO_2	CN	$CO_2C_2H_5$	COC_6H_5	$CO_2C_2H_5$	$COCH_3$	$COCH_3$
Y	H	CN	CN	CN	$CO_2C_2H_5$	$COCH_3$	COC_6H_5

When ketene mercaptals with two acyl groups, such as **3f** and **3g**, react with **1** in the ordinary manner, the products accompanied with the elimination of one of the acyl groups are obtained. This is due to the attack of methanethiol produced during the reaction on the carbonyl group of the initially formed ketene aminals **4f** and **4g**, the similar phenomena has been observed in the reaction of **3f** with *N*-methyl-1,2-ethanediamine[5]. Thus from the reaction of **3f** with **1**, **4h** is obtained, and from the reaction of **3g** with **1**, both **4h** and **4i** are obtained, but **4h** is obtained as major product, it denotes that the elimination of benzoyl group is easier than acetyl group[6]. Therefore, if one wants to obtain the ketene aminals **4f** and **4g**, the reaction should be carried out under the bubble of nitrogen gas to blow away the methanethiol as soon as it is formed.

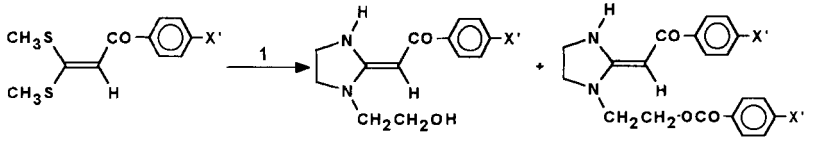


3f **4f** **4h**



3g **4g** **4h** **4i**

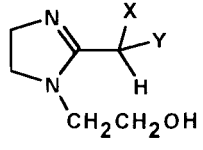
The reaction of ketene mercaptals **3i-n** with one aroyl group with **1** should be carried out in refluxing toluene. Besides ketene aminals **4i-n**, the benzoates of ketene aminals **5i-n** are also isolated from the reaction products.



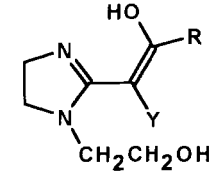
3i-n **4i-n** **5i-n**

3-5	i	j	k	l	m
X'	H	CH_3	OCH_3	Cl	Br

The constitution of all the above compounds is confirmed by elemental analyses and mass spectra. The presence of one nitrogen proton signal and the absence of methine or methylene proton signal in the ^{1}H-NMR spectra of **4** exclude the tautomeric amidine structure **B**. In the acyl substituted ketene aminals, the presence of a ketonic carbon signal in the ^{13}C-NMR spectra of these compounds also excludes the structure of tautomer **C**. The stereochemical problem of distinguishing the *E* or *Z* isomers of **4** is solved by intramolecular hydrogen bond formation. In general, compounds with intramolecular hydrogen bond are more stable. Intramolecular hydrogen bond formation is proven by the downfield shift of the nitrogen proton signal in the ^{1}H-NMR spectra, and it suggests that **4a**, **c**, **d** and **4h-n** are *E* configurated. By this method, the stereochemical problem of **4g** is still unsolved.

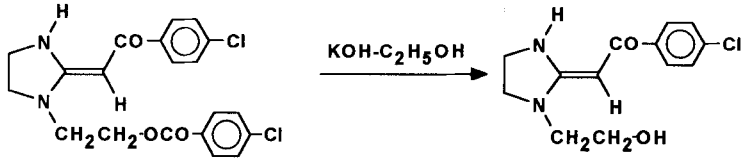


B



C

In the spectral data of compounds **5,** besides the similarity of spectral characteristics between **5** and **4,** the structure of **5** is confirmed by the appearance of a new ester carbonyl carbon signal in the ^{13}C-NMR spectra. And the structure of **5** is also verified by the hydrolysis of **5m** to **4m** .



5m **4m**

Experimental

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian Unity 200 spectrometer. IR spectra were recorded on a Perkin-Elmer 782 spectrometer for KBr tablets. UV spectra were determined with a Hitachi 340 spectrometer in methanol. Mass spectra were recorded on a AEI MS-50 instrument. Elemental analyses were performed by the Analytical Laboratory of the Institute.

(E)-1-(2-Hydroxyethyl)-2-(nitromethylene)imidazolidine (**4a**)

A solution of 4.95 g (0.03 mole) of **3a** in 30 ml of toluene was dropped into a solution of 3.12 g (0.03 mole) of **1** in 25 ml of toluene under stirring, the mixture was continuously stirred at ambient temperature for 20 h. The solid product formed was filtered out and washed successively with small amount of toluene and chloroform. The product was recrystallized from methanol, 3.81 g (73 %) of **4a** was obtained,

m.p. 173-174 °C. IR: ν = 3340 (OH), 3320 (NH), 1560, 1380 (NO_2), 1580 cm^{-1}. UV: λ_{max} = 256 nm (log ε= 4.14). ^{1}H-NMR (DMSO-d_6): δ = 8.72 (1H, s), 6.53 (1H, s), 4.90 (1H, s), 3.67, 3.64 (4H, A_2B_2), 3.54 (2H, t), 3.23 ppm (2H, t). ^{13}C-NMR (DMSO-d_6): δ = 159.1, 95.8, 58.4, 48.8, 47.8, 42.5 ppm. MS: *m/z* =173 (M^+, 14), 142 (23), 139 (13), 129 (15), 108 (30), 56 (100). Anal. calcd. for $C_6H_{11}N_3O_3$ (173.2): C 41.61, H 6.40, N 24.27; found C 41.60, H 6.37, N 24.18.

[1-(2-Hydroxyethyl)-2-imidazolidinylidene]malononitrile (**4b**).

As described for **4a**, 3.20 g (90%) of **4b** was obtained from 3.40 g (0.02 mole) of **3b** and 2.08 g (0.02 mole) of **1,** m.p. 143-144 °C (methanol). IR: ν = 3400 (OH), 3325 (NH), 2180, 2210 (CN), 1570, 1525 cm^{-1}. UV: λ_{max} = 256 nm (log ε = 4.40). ^{1}H-NMR (DMSO-d_6): δ = 7.82 (1H, s), 4.88 (1H, s), 3.61, 3.55 (4H, A_2B_2), 3.78 (2H, t), 3.45 ppm (2H, t). ^{13}C-NMR (DMSO-d_6): δ = 164.1, 118.3, 58.9, 51.4 , 48.4, 41.1, 28.1 ppm. MS: *m/z* =178 (M^+, 56), 147 (37), 135 (100), 109 (99). Anal. calcd. for $C_8H_{10}N_4O$ (178.2) : C 53.92, H 5.66, N 31.44 ; found C 53.96, H 5.51, N 31.36.

Ethyl (E)-[1-(2-Hydroxyethyl)-2-imidazolidinylidene]cyanoacetate (**4c**).

As described for **4a**, 2.20 g (90 %) of **4c** was obtained from 2.17 g (0.01 mole) of **3c** and 1.04 g (0.01 mole) of **1** , m.p. 103-104°C (dichloromethane). IR: ν = 3410 (OH), 3320 (NH), 2190 (CN), 1655(OCO), 1560, 1520 cm^{-1}. UV: λ_{max} = 261 nm(log ε =4.42). ^{1}H-NMR (DMSO-d_6): δ = 8.82 (1H, s), 4.68 (1H, s), 4.42 (2H, q), 4.15, 4.09 (4H, A_2B_2), 4.02 , 3.88 (4H, A_2B_2) , 1.54 ppm (3H, t), ^{13}C-NMR ($CDCl_3$): δ = 169.9, 164.0, 120.7, 61.0, 60.0, 52.6, 51.3, 48.9, 41.5, 14.6 ppm. ($CDCl_3$):

MS: *m/z* = 225 (M^+, 100), 182 (84), 156 (50), 148 (46), 109 (99). Anal. calcd. for $C_{10}H_{15}N_3O_3$ (225.2) : C 53.32, H 6.71, N 18.66; found C 53.46, H 6.73, N 18.63.

(E)-[1-(2-Hydroxyethyl)-2-imidazolidinylidene]benzoylacetonitrile (**4d**).

As described for **4a**, 2.20 g (86 %) of **4d** was obtained from 2.40 g (0.01 mole) of **3d** and 1.04 g (0.01 mole) of **1**, m.p. 166-167 °C. IR : ν = 3400 (OH), 3240 (NH), 2180 (CN), 1580 (CO), 1560, 1545 cm^{-1}. UV: λ_{max} =296 nm (log ε = 4.25). ^{1}H-NMR (DMSO-d_6): δ = 9.83 (1H, s), 7.34-7.62 (5H, m), 4.44 (1H, s), 3.56-3.84 ppm (8H, m), ^{13}C-NMR (DMSO-d_6): δ = 189.8, 163.6, 140.6, 129.8, 127.6, 127.4, 121.6, 64.5, 59.6, 50.4, 48.9, 41.6 ppm. MS: *m/z* = 257 (M^+, 29), 226 (7), 212 (6), 160 (14), 105 (100). Anal. calcd. for $C_{14}H_{15}N_3O_2$ (257.3): C 65.35, H 5.88, N 16.33; found C 65.39, H 5.77, N 16.42.

Diethyl [1-(2-Hydroxyethyl)-2-imidazolidinylidene]malonate (**4e**).

A solution of 2.64 g (0.01 mole) of **3e** and 1.04 g (0.01 mole) of **1** in 25 ml of toluene was refluxed for 5 h. After removal of solvent, the residue was chromatographed on silica gel column eluting with $CHCl_3$-MeOH (10:1), 1.95 g of **4e** was obtained, m.p. 73-74 °C. IR: ν = 3330 (OH , NH) , 1735 (OCO) , 1685 , 1630 , 1570 cm^{-1}. UV: λ_{max} = 270 nm (log ε = 4.18). ^{1}H-NMR ($CDCl_3$): δ = 8.53 (1H, s), 4.80 (1H, s), 4.17 (4H, q), 3.73 , 3.69 (4H, A_2B_2), 3.79 (2H, t), 3.39 (2H, t), 1.29 ppm (6H, t). ^{13}C-NMR($CDCl_3$): δ =168.4, 166.6, 72.9, 59.4 , 59.2, 50.5, 49.6, 41.3, 14.2 ppm. MS: *m/z*= 272 (M^+, 19) , 227 (28), 199 (17), 156 (48), 84 (100). Anal. calcd. for $C_{12}H_{20}N_2O_5$ (272.3): C 52.93, H 7.40, N 10.29; found C 52.65, H 7.36, N 10.26.

[1-(2-Hydroxyethyl)-2-imidazolidinylidene]acetylacetone (**4f**).

A solution of 208 mg (2 mmol) of **1** in 15 ml of toluene was cooled with ice-bath, and a solution of 420 mg (2 mmol) of **3f** in 20 ml of toluene was dropped under the bubble of nitrogen gas. Then the mixture was stirred at ambient temperature for 20 h. After removal of solvent, the residue was recrystallized from chloroform, 250 mg (59 %) of **4f** was obtained, m.p. 158-159 °C. IR : ν = 3390 (OH), 3320 (NH), 1560 (CO), 1525 cm^{-1}. UV: λ_{max} = 279 nm (log ε =4.31), 237 (3.89). ^{1}H-NMR ($CDCl_3$): δ = 9.04 (1H, s), 4.80 (1H, s), 3.88, 3.68 (4H, A_2B_2), 3.55 (2H, t), 3.22 (2H, t), 1.98 ppm (6H, s). ^{13}C-NMR (DMSO-d_6): δ = 185.7, 171.6, 95.4, 57.8, 48.3, 47.8, 41.2, 28.7 ppm. MS: *m/z* = 212 (M^+, 27), 197 (13), 181 (21), 169 (54), 155 (34), 126 (40), 56 (100). Anal. calcd. for $C_{10}H_{16}N_2O_3$ (212.3): C 56.58, H 7.60, N 13.20; found C 56.68, H 7.79, N 13.18.

[1-(2-Hydroxyethyl)-2-imidazolidinylidene]benzoylacetone (**4g**).

As described for **4f**, 420 mg (77 %) of **4g** was obtained from 530 mg (2 mmol) of **3g** and 204 mg (2 mmol) of **1**, m.p. 160-161 °C (chloroform). IR : ν = 3390 (OH), 3300 (NH), 1595, 1560 (CO), 1500 cm^{-1}. UV: λ_{max} = 307 nm (log ε = 4.02), 231 (3.77), 208 (3.79). ^{1}H-NMR ($CDCl_3$): δ = 8.93 (1H, s), 7.30-7.48 (5H, m), 4.74 (1H, s), 3.67, 3.40 (4H, A_2B_2), 3.47 (2H, t), 3.12 (2H, t), 2.07 ppm (3H, s). ^{13}C-NMR (DMSO-d_6): δ =190.0, 187.9, 169.6, 143.5, 129.3, 127.5, 127.3, 95.4, 57.7, 49.1, 47.6, 41.3, 29.5ppm. MS: *m/z* = 274 (M^+, 36), 231 (55), 215 (30), 187 (22), 159 (31), 105 (100). Anal. calcd. for $C_{15}H_{18}N_2O_3$ (274.3): C 65.67, H 6.61, N 10.21; found C 65.54, H 6.69, N 10.24.

(E)-2-(Acetylmethylene)-1-(2-hydroxyethyl)imidazolidine (**4h**).

As described for **4a**, 400 mg (47 %) of **4h** was obtained from 1.02 g (5 mmol) of **3f** and 520 mg (5 mmol) of **1** by chromatograph on a silica gel column eluting with $CHCl_3$-MeOH (100:5), m.p. 138-139°C (chloroform). IR : ν = 3260 (OH), 3200 (NH), 1585 (CO), 1545, 1500cm^{-1}. UV: λ_{max} = 287 nm (log ε = 4.46). ^{1}H-NMR ($CDCl_3$): δ = 9.23 (1H, s), 4.80 (1H, s), 3.61 (4H, t), 3.78 (2H, t), 3.30 (2H, t), 1.98 ppm (3H, s). ^{13}C-NMR (DMSO-d_6): δ = 190.9, 163.7, 75.6, 59.9, 48.6, 47.9, 42.2, 28.5ppm. MS: *m/z*=170 (M^+, 43), 155 (22), 139 (14), 126 (35), 84 (100). Anal. calcd. for $C_8H_{14}N_2O_2$ (170.2): C 56.45, H 8.29, N 16.46 ; found C 56.56, H 8.00, N 16.33.

(E)-2-(Benzoymethylene)-1-(2-hydroxyethyl)imidazolidine (**4i**) *and (E)-2-(2-Benzoylmethylene-imidazolidin-1-yl)ethyl Benzoate* (**5i**).

A solution of 3.36 g (0.015 mole) of **3i** and 1.06 g (0.015 mole) of **1** in 20 ml of toluene was refluxed for 6 h. After removal of solvent, the solid product was separated by chromatograph on silica gel column eluting with $CHCl_3$-MeOH (gradually increasing amount of MeOH from 100:2 to 100:10), 0.60 g (24 %) of **5i** and 0.65 g (19 %) of **4i** were obtained. **4i**: m.p. 117-118 °C (diethyl ether). IR: ν = 3330 (OH), 3300 (NH), 1580 (CO), 1560, 1540 cm^{-1}. UV: λ_{max} = 321 nm (log ε =4.38), 235 (4.16). ^{1}H-NMR ($CDCl_3$): δ = 9.51 (1H, s), 7.34-7.83 (5H , m), 5.28 (1H, s), 3.51 (4H, quin), 3.79 (2H, t), 3.35 ppm (2H, t). ^{13}C-NMR ($CDCl_3$): δ = 184.9, 164.6, 141.3, 129.9, 128.0, 126.6, 73.2, 60.1, 48.8, 48.2, 42.2ppm. MS: *m/z* = 232 (M^+, 30), 215 (14), 189 (34), 159 (100), 105 (90). Anal. calcd. for $C_{13}H_{16}N_2O_2$ (232.3): C 67.22, H 6.94, N 12.06;

found C 67.17, H 6.97, N 11.95. **5i**: m.p. 82-84 °C (diethyl ether). IR : ν = 3260 (NH), 1710 (OCO), 1585 (CO), 1560, 1530 cm^{-1}. UV: λ_{max} = 322 nm (log ε =4.26), 232 (4.36). ^{1}H-NMR ($CDCl_3$): δ = 9.73 (1H, s), 7.38-8.05 (5H, m), 7.30-7.84 (5H, m), 5.37 (1H, s), 3.70 (4H, t), 4.52 (2H, t), 3.67 ppm (2H, t). ^{13}C-NMR ($CDCl_3$): δ = 185.5, 166.4, 164.4, 141.4, 133.3, 131.6, 129.8, 129.6, 128.4, 128.0, 126.6, 73.2, 62.0, 48.3, 44.6, 42.0 ppm. MS: *m/z* = 336 (M+, 24) , 231 (79), 215 (40), 159 (36), 105 (100). Anal. calcd. for $C_{20}H_{20}N_2O_3$ (336.4): C 71.41, H 5.99, N 8.33; found C 71.35, H 5.90, N 8.30.

(E)-1-(2-Hydroxyethyl)-2-[(4-methylbenzoyl)methylene]imidazolidine (**4j**) *and (E)-2-[(4-Methylbenzoyl)-methylene-imidazolidin-1-yl]ethyl 4-Methylbenzoate* (**5j**).

A solution of 7.14 g (0.03 mole) of **3j** and 3.01 g (0.03 mole) of **1** in 30 ml of toluene was refluxed for 6 h. After cooling, 3.10 g of **4j** was filtered out. The mother liquid was chromatographed on a silica gel column, and 1.20 g (22%) of **5j** was obtained by elution with ethyl acetate and a more 0.87 g of **4j** was obtained by elution with ethyl acetate-acetone (2:1), the total yield of **4j** was 3.97 g (54%). **4j**: m.p. 156-157 °C (ethyl acetate-acetone) . IR : ν = 3300 (OH), 3250 (NH), 1580 (CO), 1565, 1540 cm^{-1}. UV: λ_{max} = 321 nm (log ε =4.40), 240 (4.11). ^{1}H-NMR ($CDCl_3$): δ = 9.40 (1H, s), 7.69 (2H, d), 7.13 (2H, d), 5.24 (1H, s), 3.46 (4H, s), 3.74 (2H, t), 3.29 (2H, t), 2.32 ppm (3H, s). ^{13}C-NMR ($CDCl_3$): δ = 184.5, 164.5, 140.1, 138.5, 128.7, 126.6, 73.1, 59.9, 48.7, 48.2, 42.1 , 21.4 ppm. MS: *m/z* = 246 (M+, 42), 229 (11), 203 (58), 173 (100), 119(85). Anal. calcd. for $C_{14}H_{18}N_2O_2$ (246.3): C 68.27, H 7.37, N 11.38; found C 68.19, H 7.26, N 11.32. **5j**: m.p. 110-111 °C (ethanol). IR : ν = 3270 (NH), 1705 (OCO), 1585 (CO), 1565, 1530

cm^{-1}. UV: λ_{max} = 322 nm (log ε =4.38), 239 (4.48). ^{1}H-NMR ($CDCl_3$): δ = 9.67 (1H, s), 7.87 (2H, d), 7.13 (2H, d), 7.69 (2H, d), 7.12 (2H, d), 5.35 (1H, s), 3.61 (4H, t), 4.44 (2H, t), 3.58 (2H, t), 2.34 ppm (6H, s). ^{13}C-NMR ($CDCl_3$): δ = 185.9, 166.4, 164.5, 144.0, 140.1, 140.0, 139.0, 129.9, 129.8, 128.9, 126.8, 72.7, 61.7, 48.4, 44.7, 42.3, 21.7, 21.4 ppm. MS: *m/z*= 364 (M+, 34), 245 (83), 229 (38), 174 (31), 119 (100). Anal. calcd. for $C_{22}H_{24}N_2O_3$ (364.4): C 72.50, H 6.44, N 7.69; found C 72.44, H 6.57, N 7.61.

(E)-1-(2-Hydroxyethyl)-2-[(4-methoxybenzoyl)methylene]imidazolidine(**4k**) *and (E)-2-[(4-Methoxybenzoyl)-methylene-imidazolidin-1-yl]ethyl 4-Methoxybenzoate* (**5k**).

A solution of 7.63 g (0.03 mole) of **3k** and 3.12 g (0.03 mole) of **1** in 30 ml of toluene was refluxed for 6 h. After removal of solvent, the residue was chromatographed on a silica gel column, 1.05 g (18 %) of **5k** was obtained by elution with chloroform and 1.70 g (22 %) of **4k** was obtained by elution with $CHCl_3$-MeOH (10:1). **4k**: m.p. 139-140 °C. IR: ν = 3300 (OH), 3295 (NH), 1575 (CO), 1565, 1540 cm^{-1}. UV: λ_{max} = 324 nm (log ε= 4.45), 251 (4.48) . ^{1}H-NMR ($CDCl_3$): δ = 9.30 (1H, s), 7.72 (2H, d), 6.80 (2H, d), 5.18 (1H, s), 3.74 (3H, s), 3.40 (4H, s), 3.67 (2H, t), 3.23 ppm (2H, t) . ^{13}C-NMR ($CDCl_3$): δ = 183.7, 164.2, 160.8, 133.7 , 128.0, 113.0, 72.5, 59.5, 55.0, 48.4, 47.9, 41.9 ppm. MS: *m/z*=262 (M^+, 39), 219 (31), 190 (50), 135 (100). Anal. calcd. for $C_{14}H_{18}N_2O_3$ (262.3): C 64.10, H 6.92, N 10.68; found: C 63.86, H 7.13, N 10.73. **5k**: m.p. 117-119 °C (dichloromethane-diethyl ether). IR : ν = 3240 (NH), 1700 (OCO), 1585 (CO), 1560, 1525 cm^{-1}. UV: λ_{max} = 325 nm (log ε =4.42), 256 (4.44). ^{1}H-NMR ($CDCl_3$): δ = 9.69 (1H, s), 7.94 (2H, d), 6.85 (2H, d), 7.78 (2H, d), 6.78 (2H, d), 5.32 (1H, s), 3.66 (4H, t),

4.46 (2H, t), 3.64 (2H, t), 3.82 (3H, s), 3.78 ppm (3H, s). ^{13}C-NMR ($CDCl_3$): δ =184.9, 166.1, 164.3, 163.5, 161.0, 134.0, 133.8, 131.7, 128.3, 113.6, 113.1, 72.2, 55.3, 55.2, 61.6, 48.3, 44.7, 42.2 ppm. MS: *m/z*=396 (M^+, 25), 261 (53), 245 (19), 190 (24), 135 (100). Anal. calcd. for $C_{22}H_{24}N_2O_5$ (396.4): C 66.65, H 6.10, N 7.07; found C 66.54, H 6.01, N 7.06.

(E)-2-[(4-Chlorobenzoyl)methylene]-1-(2-hydroxyethyl)imidazolidine (**4m**) *and (E)-2-[(4-Chlorobenzoyl)-methylene-imidazolidin-1-yl]ethyl 4-Chlorobenzoate* (**5m**).

A solution of 7.76 g (0.03 mole) of **3m** and 3.12 g (0.03 mole) of **1** in 30 ml of toluene was refluxed for 6 h. After removal of partial solvent, 1.80 g of **5m** was obtained by addition of petroleum ether (60-90 °C) after cooling. The mother liquid was chromatographed on a silica gel column by elution with ethyl acetate-acetone (gradually increasing the amount of acetone from 100:5 to 100:10), a more 0.28 g of **5m** and 0.47 g (6%) **4m** were obtained, the total yield of **5m** was 2.08 g (34%). **4m**: m.p. 154-156 °C (ethanol). IR: ν = 3290 (OH), 3240 (NH), 1580 (CO), 1565, 1540 cm^{-1}. UV: λ_{max} = 324 nm (log ε = 4.36), 242 (4.24). ^{1}H-NMR ($CDCl_3$): δ = 9.42 (1H, s), 7.75 (2H, d), 7.33 (2H, d), 5.20 (1H, s), 3.52 (4H, quin), 3.75 (2H, t), 3.35 ppm (2H, t). ^{13}C-NMR ($CDCl_3$): δ = 183.5, 164.7, 139.6, 135.9, 128.5, 128.4, 73.2, 60.0, 48.8, 48.1, 42.2 ppm. MS: *m/z* = 268 (14), 266 (M^+, 42), 249 (14), 223 (54), 193 (100), 139 (68). Anal. calcd. for $C_{13}H_{15}ClN_2O_2$ (266.7): C 58.54, H 5.87, N 10.51, Cl 13.29; found C 58.55, H 5.66, N 10.62, Cl 13.32. **5m**: m.p. 172-174 °C (chloroform-petroleum ether). IR : ν = 3270 (NH), 1710 (OCO), 1580 (CO), 1565, 1535 cm^{-1}. UV: λ_{max} = 325 nm (log ε= 4.34), 240 (4.57). ^{1}H-NMR ($CDCl_3$): δ = 9.70 (1H, s), 7.97 (2H,

d), 7.45 (2H, d), 7.92 (2H, d), 7.44 (2H, d), 5.22 (1H, s), 3.78 (4H, t), 4.52 (2H, t), 3.69 ppm (2H, t). ^{13}C-NMR ($CDCl_3$): δ = 184.1, 165.5, 164.4, 139.7, 135.3, 135.2, 133.8, 131.0, 128.8, 128.1, 128.0, 72.8, 61.8, 48.1, 44.5, 42.2 ppm. MS: *m/z* =406 (18), 404 (M^+, 29), 265 (100), 249 (47), 194 (36), 139 (85). Anal. calcd. for $C_{20}H_{18}Cl_2N_2O_3$ (405.3): C 59.27, H 4.48, N 6.91, Cl 17.50; found C 59.20, H 4.27, N 6.86, Cl 17.68.

(E)-2-[(4-Bromobenzoyl)methylene]-1-(2-hydroxyethyl)imidazolidine (**4n**) *and (E)-2-[(4-Bromobenzoyl)-methylene-imidazolidin-1-yl]ethyl 4-Bromobenzoate* (**5n**).

A solution of 9.03 g (0.03 mole) of **3n** and 3.12 g (0.03 mole) of **1** in 30 ml of toluene was refluxed for 6 h. After cooling, the solid product was filtered out and recrystallized from acetone, 0.50 g of **5n** was obtained, then the residue was recrystallized from ethanol, 1.03 g of **4n** was obtained. The mother liquid was chromatographed on a silica gel column, and a more 0.62 g of **5n** was obtained by elution with ethyl acetate, and a more 0.31 g of **4n** was obtained by elution with ethyl acetate-acetone. The total yield of **4n** was 1.34 g (14 %) and that of **5n** was 1.42 g (19%). **4n**: m.p. 158-159 °C (ethanol). IR : ν = 3290 (OH), 3240 (NH), 1575 (CO), 1560, 1540 cm^{-1}. UV: λ_{max} = 325 nm (log ε= 4.35), 244 (4.23). ^{1}H-NMR ($CDCl_3$): δ = 9.58 (1H, s), 7.68 (2H, d), 7.47 (2H, d), 5.23 (1H, s), 3.58 (4H, quin), 3.78 (2H, t), 3.35 ppm (2H, t). ^{13}C-NMR ($CDCl_3$): δ = 183.8, 164.8, 139.9, 131.2, 128.6, 124.5, 73.3, 59.9, 48.8, 48.2, 42.3 ppm. MS: *m/z* = 312 (43), 310 (M^+, 43), 267 (50), 238 (90), 183 (54), 56 (100). Anal. calcd. for $C_{13}H_{15}BrN_2O_2$ (311.2): C 50.17, H 4.86, N 9.00, Br 25.68; found C 50.14, H 4.71, N 8.96, Br 25.66. **5n**: m.p. 176-177 °C (acetone). IR : ν = 3280 (NH), 1710 (OCO), 1580 (CO), 1565, 1535 cm^{-1}. UV: λ_{max} = 327 nm

(log ε = 4.30), 244 (4.58). ^{1}H-NMR ($CDCl_3$): δ = 9.68 (1H, s), 7.82 (2H, d), 7.46 (2H, d), 7.64 (2H, d), 7.45 (2H, d), 5.24 (1H, s), 3.67 (4H, t), 4.50 (2H, t), 3.64 ppm (2H, t). ^{13}C-NMR ($CDCl_3$): δ = 184.1, 165.7, 164.4, 140.3, 140.2, 131.8, 131.2, 131.1 , 128.6, 128.3, 124.2, 73.0, 61.9, 48.2, 44.6, 42.2 ppm. MS: *m/z* = 494 (39), 492 (M^+, 22), 309 (100), 293 (56), 238 (38), 183 (85). Anal. calcd. for $C_{20}H_{18}Br_2N_2O_3$ (494.2): C 48.61, H 3.67, N 5.67, Br 32.34; found C 48.64, H 3.64, N 5.38, Br 32.47.

Hydrolysis of **5m** *to* **4m.**

A solution of 405 mg (1 mmol) of **5m** and 62 mg (1.1 mmol) of potassium hydroxide in 15 ml of ethanol was stirred at ambient temperature for 5 h. After removal of solvent, the residue was washed with ethyl acetate- petroleum ether, 220 mg (82 %) of **4m** was obtained.

Reaction of **3g** *with* **1**.

A solution of 2.13 g (8 mmol) of **3g** in 10 ml of toluene was dropped into a solution of 0.83 g (8mmol) of **1** in 20 ml of toluene, and the mixture was stirred at ambient temperature for 48 h. After removal of solvent, the residue was chromatographed on a silica gel column eluting with $CHCl_3$-MeOH (gradually increasing the amount of MeOH from 100:8 to 100:20), 0.63 (37 %) of **4h** and 0.27 (12 %) of **4i** were obtained.

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